(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 November 2016 (24.11.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/187347 A1

(51) International Patent Classification:
A61P 5/00 (2006.01) *A61K 45/06* (2006.01)
A61P 5/46 (2006.01)

(21) International Application Number:
PCT/US2016/033143

(22) International Filing Date:
18 May 2016 (18.05.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/163,130 18 May 2015 (18.05.2015) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2016/187347 A1

(54) **Title**: METHODS FOR DIAGNOSING AND ASSESSING TREATMENT FOR CUSHING'S SYNDROME

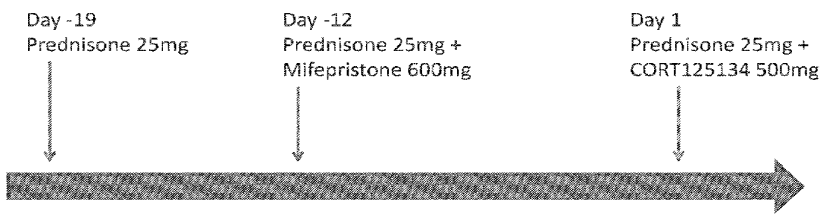

FIG. 1

(57) **Abstract**: Methods are provided for assessing a clinical response to a glucocorticoid receptor antagonist (GRA) in a human subject and for diagnosing Cushing's syndrome.

METHODS FOR DIAGNOSING AND ASSESSING TREATMENT FOR CUSHING'S SYNDROME

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/163,130, filed on May 18, 2015, the contents of which are hereby incorporated in the entirety for all purposes.

BACKGROUND OF THE INVENTION

[0002] Glucocorticoids (GCs) are a class of steroid hormones that bind to and activate the glucocorticoid receptor (GR), which is present in almost every vertebrate cell. The GR is pleiotropic and regulates a variety of important pathways in the vertebrate organism, for example, metabolism, immunity, and development. As such, detection of GR activity or regulation can be used to diagnose a variety of different vertebrate diseases, or assess a clinical or biochemical response to treatments that modulate GR activity.

[0003] For example, detection of GR activity or regulation can be used for detection of various forms of Cushing's syndrome. As another example, glucocorticoid receptor antagonists (GRAs) can be administered to a patient to treat a number of different diseases and conditions, and detection of a change in GR activity in response to administration of the GRA can indicate or assess a clinical or biochemical response to the treatment. However, current methods and compositions for assessing GR activity suffer from one or more of the following insufficiencies: high cost, low sensitivity, low specificity, high false positive rate, or high false negative rate. Therefore, there remains a need for improved methods and compositions for detection of GR activity.

BRIEF SUMMARY OF THE INVENTION

[0004] In a first aspect, the present invention provides a method for assessing a clinical or biochemical response to a glucocorticoid receptor antagonist (GRA) in a human subject, the method comprising: a) measuring a first amount, or activity of 51 kDa FK506 binding protein

(FKBP5 protein) or a first expression level of a gene encoding FKBP5 protein in a first sample from the subject, wherein: i) the first sample comprises primary cells; and ii) the first sample is or was obtained before administering the GRA to the subject; b) optionally administering the GRA to the subject; c) measuring a second amount or activity of FKBP5 protein or a second expression level of a gene encoding FKBP5 protein in a second sample from the subject, wherein: i) the second sample comprises primary cells; and ii) the second sample is or was obtained after administering the GRA to the subject; and d) comparing the first and second amounts, activities, or expression levels, wherein a reduction in the amount or activity of FKBP5 protein or a reduction in the expression level of the gene encoding FKBP5 protein in the second sample as compared to the first sample indicates the clinical or biochemical response to the GRA. In some cases, the absence of a reduction indicates a lack of a clinical response or a lack of biochemical response to the GRA.

[0005] In a second aspect, the present invention provides a method for assessing a clinical or biochemical response to a GRA in a human subject, the method comprising: a) measuring a first amount, or activity of 51 kDa FK506 binding protein (FKBP5 protein) or a first expression level of a gene encoding FKBP5 protein in a first sample from the subject, wherein: i) the first sample comprises primary cells; and ii) the first sample is or was obtained before administering the GRA to the subject; b) optionally administering the GRA to the subject; c) measuring a second amount or activity of FKBP5 protein or a second expression level of a gene encoding FKBP5 protein in a second sample from the subject, wherein: i) the second sample comprises primary cells; and ii) the second sample is or was obtained after administering the GRA to the subject; d) comparing the first and second amounts, activities, or expression levels to obtain an FKBP5 difference value; e) comparing the difference value to a threshold difference value derived from a cohort of at least 20 or 30 or 50 test individuals; and f) identifying the subject as having or not having the clinical or biochemical response to the GRA based on a comparison of the difference value and threshold difference value. In some cases, the threshold difference value is a threshold reduction value and a presence of a reduction in FKBP5 amount or activity between the first and second sample that is greater than a threshold reduction value indicates a clinical or biochemical response to the GRA. In some cases, the threshold difference value is a threshold reduction value and a presence of a reduction in FKBP5 amount or activity between the first and second sample that is similar to (*e.g.*, within about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, or 70% of) a threshold reduction value indicates a clinical or biochemical response to

the GRA. In some cases, the at least 20 or 30 or 50 test individuals are subjects known to have or suspected of having Cushing's syndrome. In some cases, the threshold difference value is determined by subtracting a post-GRA administration FKBP5 amount, activity, or expression from a pre-GRA administration FKBP5 amount, activity, or expression in a cohort of 20 or 30 or 50 test individuals known to have or suspected of having Cushing's syndrome that is controlled or well-controlled by GRA administration.

[0006] In some embodiments, the subject is administered a GRA in multiple doses and the first sample is obtained prior to administering the multiple doses of GRA and the second sample is obtained after administering the multiple doses of GRA to the subject. In some embodiments the measuring of a) and/or c) comprises quantitating an amount of mRNA encoding FKBP5 protein in the sample. In some embodiments, the measuring of a) and/or c) comprises quantitating the amount of FKBP5 protein in the sample. In some embodiments the measuring comprises quantitating the amount of FKBP5 protein activity in the sample. In some embodiments, the quantitating the amount of FKBP5 protein activity in the sample comprises measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample. In some embodiments, the quantitating the amount of FKBP5 protein activity in the sample comprises measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample.

[0007] In some embodiments, the administering the GRA to the subject comprises administering mifepristone to the subject. In some embodiments, the administering the GRA to the subject comprises administering a GRA that is not mifepristone to the subject. In some embodiments, the administering the GRA to the subject comprises administering a heteroaryl-ketone GRA. In some embodiments, the first or second samples comprise whole blood, or a fraction thereof. In some embodiments, the first and second samples comprise whole blood, or a fraction thereof. In some embodiments, the first or second samples comprise nasal epithelial scraping samples. In some embodiments, the patient is in need of administration of the glucocorticoid receptor antagonist (GRA). In some embodiments, the patient has elevated levels of cortisol.

[0008] In some embodiments, the patient has cancer and the first and second samples comprise tumor cells. In some embodiments, the first or second samples comprise whole blood, or a fraction thereof. In some embodiments, the first and second samples comprise whole blood, or a fraction thereof. In some embodiments, the method comprises

administering an increased amount of GRA to the subject in the absence of a detected reduction in the amount or activity of FKBP5 protein or a detected reduction in the expression level of the gene encoding FKBP5 protein in the second sample.

[0009] In a third aspect, the present invention provides a method for diagnosing Cushing's syndrome in a human subject, the method comprising: a) measuring an amount, or activity of 51 kDa FK506 binding protein (FKBP5 protein) or an expression level of a gene encoding FKBP5 protein in a sample obtained or provided from the subject, wherein the sample comprises primary cells; and b) identifying the subject as likely to be suffering from Cushing's syndrome when the amount, activity or expression level is high relative to a control. In some cases, the control comprises a value derived from at least 100 or at least 200 test individuals. In some cases, the test individuals are subjects that are known to not exhibit Cushing's syndrome. In some cases, the test individuals are subjects that are known to have normal cortisol levels or are known to lack hypercortisolemia. In some cases, the control comprises a value derived from at least 20 or 30 or 50 test individuals. In some cases, the test individuals are subjects diagnosed with Cushing's syndrome and undergoing therapy with a GRA. In some cases, the test individuals are subjects diagnosed with Cushing's syndrome, undergoing therapy with a GRA, wherein at least one symptom of the Cushing's syndrome is mitigated or eliminated by the GRA therapy.

[0010] In a fourth aspect, the present invention provides a method for assessing a clinical or biochemical response to a GRA in a human subject, the method comprising: a) measuring an amount, or activity of 51 kDa FK506 binding protein (FKBP5 protein) or an expression level of a gene encoding FKBP5 protein in a sample from the subject, wherein: i) the sample comprises primary cells; and ii) the sample is or was obtained after administering the GRA to the subject; d) comparing the amount, activities, or expression level of FKBP5 to a control value derived from a cohort of at least 100 or at least 200 test individuals; and f) identifying the subject as having or not having the clinical or biochemical response to the GRA based on a comparison of the FKBP5 amount, activity or expression level to the control value. In some cases, the at least 100 or at least 200 test individuals are normal subjects that are not otherwise in need of a GRA. In some cases, the at least 100 or at least 200 test individuals do not have Cushing's syndrome. In some cases, the at least 100 or at least 200 test individuals do not have elevated levels of cortisol. In some cases, the at least 100 or at least 200 test individuals do not have, or do not exhibit symptoms of hypercortisolemia.

[0011] In some embodiments, the measuring comprises quantitating an amount of mRNA encoding FKBP5 protein in the primary cells of the sample. In some embodiments, the measuring comprises quantitating the amount of FKBP5 protein in the primary cells of the sample. In some embodiments, the measuring comprises quantitating the amount of FKBP5 protein activity in the primary cells of the sample. In some embodiments, the quantitating the amount of FKBP5 protein activity in the primary cells of the sample comprises quantitating FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the primary cells of the sample. In some embodiments, the quantitating the amount of FKBP5 protein activity in the primary cells of the sample comprises quantitating the amount of FKBP5 protein bound to GR in the primary cells of the sample. In some embodiments, the sample obtained from the subject comprises whole blood, or a fraction thereof. In some embodiments, the subject has undergone transsphenoidal surgery before the sample is obtained from the subject. In some embodiments, the sample is obtained from the subject less than eleven days after the subject is treated with transsphenoidal surgery. In some embodiments, the sample is obtained from the subject less than two, four, or six weeks after the subject is treated with transsphenoidal surgery. In some embodiments, the method comprises administering a treatment for Cushing's syndrome when the amount or activity of FKBP5 protein or the expression level of the gene encoding FKBP5 protein is high relative to a control. In some cases, the administering the treatment for Cushing's syndrome comprises administering to the subject a glucocorticoid receptor antagonist (GRA)

[0012] In a fifth aspect, the present invention provides a method for assessing a clinical or biochemical response in a human subject to administering to the subject a medical or surgical therapy for treatment of hypercortisolemia, the method comprising: a) measuring a first amount, or activity of 51 kDa FK506 binding protein (FKBP5 protein) or a first expression level of a gene encoding FKBP5 protein in a first sample from the subject, wherein: i) the first sample comprises primary cells; and ii) the first sample is or was obtained before administering the medical or surgical therapy for treatment of hypercortisolemia to the subject; b) optionally administering the medical or surgical therapy for treatment of hypercortisolemia to the subject; c) measuring a second amount or activity of FKBP5 protein or a second expression level of a gene encoding FKBP5 protein in a second sample from the subject, wherein: i) the second sample comprises primary cells; and ii) the second sample is or was obtained after administering the medical or surgical therapy for treatment of hypercortisolemia to the subject; and d) comparing the first and second amounts, activities, or

expression levels, wherein a reduction in the amount or activity of FKBP5 protein or a reduction in the expression level of the gene encoding FKBP5 protein in the second sample indicates the clinical response or the biochemical response to the medical or surgical therapy for treatment of hypercortisolemia. For example, a reduction in the amount or activity of FKBP5 protein or a reduction in the expression level of the gene encoding FKBP5 protein in the second sample can indicate that the medical or surgical therapy is successful in treating the hypercortisolism.

[0013] In a sixth aspect, the present invention provides a method for assessing a clinical or biochemical response to administering to the subject a medical or surgical therapy for treatment of hypercortisolemia, the method comprising: a) measuring a first amount, or activity of 51 kDa FK506 binding protein (FKBP5 protein) or a first expression level of a gene encoding FKBP5 protein in a first sample from the subject, wherein: i) the first sample comprises primary cells; and ii) the first sample is or was obtained before administering the GRA to the subject; b) optionally administering the medical or surgical therapy for treatment of hypercortisolemia to the subject; c) measuring a second amount or activity of FKBP5 protein or a second expression level of a gene encoding FKBP5 protein in a second sample from the subject, wherein: i) the second sample comprises primary cells; and ii) the second sample is or was obtained after administering the GRA to the subject; d) comparing the first and second amounts, activities, or expression levels to obtain an FKBP5 difference value; e) comparing the difference value to a threshold difference value derived from a cohort of at least 20 or 30 or 50 test individuals; and f) identifying the subject as having or not having the clinical or biochemical response to the GRA based on a comparison of the difference value and threshold difference value. In some cases, the threshold difference value is a threshold reduction value and a presence of a reduction in FKBP5 amount or activity between the first and second sample that is greater than, or similar to, a threshold reduction value indicates a clinical or biochemical response to the GRA. In some cases, the at least 20 or 30 or 50 test individuals are subjects known to have or suspected of having Cushing`s syndrome.

[0014] In some embodiments, the medical or surgical therapy for treatment of hypercortisolemia is selected from the group consisting of: inhibition of steroidogenesis, administration of an ACTH modulator, GRA administration, : transsphenoidal surgery, repeat transsphenoidal surgery, unilateral adrenalectomy, bilateral adrenalectomy, radiotherapy, resection of a non-pituitary ACTH-secreting tumor, treatment with a peptide receptor radionuclide therapy, and combinations thereof. In some embodiments, the inhibition of

steroidogenesis comprises administration of ketoconazole, levoketoconazole, metyrapone, LCI699, mitotane, aminoglutethimide, etomidate, or a combination thereof. In some embodiments, the administration of an ACTH modulator comprises administration of a dopamine agonist, somatostatin, a somatostatin analog, retinoic acid, R-roscovitine, or a combination thereof. In some embodiments, the dopamine agonist is selected from the group consisting of bromocriptine and cabergoline. In some embodiments, the method comprises administering an additional medical or surgical therapy for treatment of hypercortisolemia in an absence of a detected reduction in the amount or activity of FKBP5 protein or reduction in the expression level of the gene encoding FKBP5 protein in the second sample.

[0015] In some embodiments the measuring of a) and/or c) comprises quantitating an amount of mRNA encoding FKBP5 protein in the sample. In some embodiments, the measuring of a) and/or c) comprises quantitating the amount of FKBP5 protein in the sample. In some embodiments the measuring comprises quantitating the amount of FKBP5 protein activity in the sample. In some embodiments, the quantitating the amount of FKBP5 protein activity in the sample comprises measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample. In some embodiments, the quantitating the amount of FKBP5 protein activity in the sample comprises measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample.

[0016] In some embodiments, the GRA administration comprises administering mifepristone to the subject. In some embodiments, the GRA administration comprises administering a GRA that is not mifepristone to the subject. In some embodiments, GRA administration comprises administering a heteroaryl-ketone GRA. In some embodiments, the first or second samples comprise whole blood, or a fraction thereof. In some embodiments, the first and second samples comprise whole blood, or a fraction thereof. In some embodiments, the first or second samples comprise nasal epithelial scraping samples. In some embodiments, the patient is in need of a medical or surgical therapy for treatment of hypercortisolemia. In some embodiments, the patient has elevated levels of cortisol.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] **FIG. 1**: depicts a study scheme for examining the expression level of the gene FKBP5, which encodes the FKBP5 protein, in response to administration of a GR modulator. In this scheme, healthy subjects are administered a GR agonist, followed by co-

administration of a GR agonist and a GR antagonist (GRA). Blood samples are obtained from 10 subjects before each dose and at various time points after each dose. FKBP5 expression levels are measured before dosing on each day, and at selected times after dosing on each day.

[0018] **FIG. 2**: depicts the fold difference in GAPDH normalized FKBP5 expression levels in samples taken before and after administration of the indicated GR agonist (prednisone), or before and after administration of the indicated GR agonist in combination with the indicated GR antagonist (mifepristone or CORT125134).

DEFINITIONS

[0019] The abbreviations used herein have their conventional meaning within the chemical and biological arts. As used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

[0020] As used herein, "glucocorticoid receptor" ("GR") refers to the type II GR or nuclear receptor subfamily 3, group C, member 1 (NR3C1), which specifically binds to cortisol and/or cortisol analogs such as dexamethasone (*See, e.g.*, Turner & Muller, J Mol Endocrinol October 1, 2005 35 283-292). The GR is also referred to as the cortisol receptor. The term includes isoforms of GR, recombinant GR and mutated GR.

[0021] "Glucocorticoid receptor antagonist" ("GRA") refers to any composition or compound which partially or completely inhibits (antagonizes) the binding of a glucocorticoid receptor (GR) agonist, such as cortisol, or cortisol analogs, synthetic or natural, to a GR. A "specific glucocorticoid receptor antagonist" refers to any composition or compound which inhibits any biological response associated with the binding of a GR to an agonist. By "specific," the drug preferentially binds to the GR rather than other nuclear receptors, such as mineralocorticoid receptor (MR), androgen receptor (AR), or progesterone receptor (PR). It is preferred that the specific glucocorticoid receptor antagonist bind GR with an affinity that is 10-fold greater ($1/10^{th}$ the K_d value) than its affinity to the MR, AR, or PR, both the MR and PR, both the MR and AR, both the AR and PR, or to the MR, AR, and PR. In a more preferred embodiment, the specific glucocorticoid receptor antagonist binds GR with an affinity that is 100-fold greater ($1/100^{th}$ the K_d value) than its affinity to the MR, AR, or PR, both the MR and PR, both the MR and AR, both the AR and PR, or to the MR, AR, and PR.

[0022] "Human subject" refers to a human primate. The human subject can be a person having, or suspected of having, Cushing's syndrome or a disease or condition that can be treated with a GRA. Similarly, "a patient in need of administration of a glucocorticoid receptor antagonist (GRA)" can be a person having or, or suspected of having, Cushing's syndrome or a disease or condition that can be treated with a GRA. Exemplary diseases or conditions that can be treated with a GRA include, but are not limited to cancer, breast cancer, triple negative breast cancer, prostate cancer, metastatic prostate cancer, ovarian cancer, Cushing's syndrome, or Cushing's disease. In some cases, the human subject can be a person that has been previously treated with transsphenoidal surgery (*e.g.*, to remove tumors of the pituitary gland, such as pituitary adenomas). For example the subject may have undergone transsphenoidal surgery to treat Cushing's disease. In some cases, the human subject previously treated with transsphenoidal surgery can be a subject that has undergone transsphenoidal surgery less than, or less than about, 20 days, 19 days, 18 days, 17 days, 16 days, 15 days, 14 days, 13 days, 12 days, 11 days, 10 days, 9 days, 8 days, 7 days, 6 days, 5 days, 4 days, 3 days, 2 days, or 1 day ago.

[0023] "Assessing a clinical or biochemical response to a glucocorticoid receptor antagonist (GRA)" refers to detecting or quantifying a response to an administered GRA. The clinical response can be an indication that the GRA is likely to be successful in treating a disease or condition, or successful in mitigating or ameliorating one or more symptoms of a disease or condition. The biochemical response can be an indication that the GRA is at a dose that is sufficient to alter, or significantly alter, the physiology of the subject to which the GRA is administered. The biochemical response can be an indication that the GRA is likely to be successful in treating a disease or condition, or successful in mitigating or ameliorating one or more symptoms of a disease or condition. The disease or condition can be, *e.g.*, hypercortisolemia or Cushing's syndrome. The clinical or biochemical response can be assessed by detecting a change in GR activity or regulation caused by or correlated with administration of a GRA. For example, a change in the amount or activity of FKBP5 protein, or the expression level of a gene encoding FKBP5 protein, in response to administration of a GRA can be detected to assess a clinical response or a biochemical response to a GRA.

[0024] "Assessing a clinical or biochemical response to administering a medical or surgical therapy for treatment of hypercortisolemia" and the like, refers to detecting or quantitating a response to the administered therapy. The clinical response can be an indication that the therapy is likely to be successful in treating the hypercortisolemia, or successful in mitigating

or ameliorating one or more symptoms of the hypercortisolemia. The biochemical response can be an indication that the administered therapy has altered, or significantly altered, the physiology of the subject to which the therapy is administered. The biochemical response can be an indication that the therapy is likely to be successful in treating the hypercortisolemia, or successful in mitigating or ameliorating one or more symptoms of the hypercortisolemia.

[0025] "Measuring an amount or activity of FKBP5 protein" refers to measuring the amount of FKBP5 protein or measuring the amount of an activity of the FKBP5 protein in a sample. The activity can be *cis-trans* prolyl isomerase activity, FK506 or rapamycin binding activity, GR binding activity, or chaperone activity (*e.g.*, steroid hormone chaperone activity).

[0026] "Measuring an expression level of a gene encoding FKBP5 protein" generally refers to measurement of the amount of mRNA encoding FKBP5 protein in a sample, or measuring the production of mRNA encoding FKBP5 protein in the sample. Methods for measuring mRNA or mRNA production include, but are not limited to, RT-PCR, digital RT-PCR, RNA-seq (*e.g.*, Methods Mol Biol. 2014;1158:71-91), and microarray analysis.

[0027] "Primary cells" refers to cells that have not been immortalized or passaged more than one time. Primary cells include human cells that have been taken directly from an individual without any subsequent culturing or division.

[0028] "Sample" refers to a biological sample obtained from any tissue or organ of a human subject. The sample can be any cell or tissue sample from a human subject. Samples can be subject to various treatment, storage or processing procedures before being analyzed according to the methods described herein. Generally, the terms "sample" or "samples" are not intended to be limited by their source, origin, manner of procurement, treatment, processing, storage or analysis, or any modification. The biological sample can contain primary cells originating from a human subject. The sample can contain an FKBP5 polypeptide or portion thereof, a nucleic acid encoding an FKBP5 polypeptide or portion thereof, an amplification or reverse transcription product of a nucleic acid encoding an FKBP5 polypeptide or portion thereof, or combination of any two or more of the foregoing polypeptides, nucleic acids, amplification products, reverse transcription products, or portions thereof.

[0029] "Whole blood" refers to blood collected from a human subject that is not subject to serum or plasma separation. "A fraction thereof" in the context of such whole blood refers to any fraction of whole blood, such as plasma, serum, a leukocyte fraction, a red blood cell fraction, a sample of peripheral blood mononuclear cells, and the like.

[0030] "Control" or "control value" in the context of amount or activity of FKBP5 protein, expression levels of the FKBP5 gene, or a fold-change in FKBP5 amount, activity, or expression level, can refer to a level that is typically found in a subject under various clinical conditions. For example, the control value can be an amount typically found in a Cushing's patient. As another example, the control value can be an amount typically found in a healthy (*e.g.*, non-Cushing's) patient. As another example, the control value can be a fold-change typically observed when a patient or cells of a patient are administered a GRA (*e.g.*, at a typical dose), wherein the patient or cells of the patient exhibit a clinical response to the GRA or exhibit a biochemical response to the GRA. As another example, a control value can be a fold-change that is typically observed when a patient or cells of a patient are administered a GRA (*e.g.*, at a typical dose), wherein the patient or cells of the patient that do not exhibit a clinical response to the GRA or do not exhibit a biochemical response to the GRA.

[0031] In some cases, the control value is a normalized control value. The normalized control value can be normalized against a house keeping gene (*e.g.*, GAPDH) or protein, or normalized against total protein or RNA (*e.g.*, mRNA) levels as described herein. In some cases, the control value is an absolute value, or an absolute value per sample volume, or per number of cells in a sample.

DETAILED DESCRIPTION OF THE INVENTION

I. Introduction

[0032] The 51-kDa FK506 binding protein (FKBP51 or FKBP5) is part of the immunophilin family, a superfamily of highly conserved proteins first characterized by their ability to bind to immunosuppressant drugs (Barik, 2006; Baughman *et al.*, 1995). In addition to their drug binding capabilities, some FK506 binding immunophilins are also protein chaperones, and have the related but apparently separate ability to isomerize proline residues (PPIase activity) (Barik, 2006).

[0033] The FKBP5 protein is an hsp90 co-chaperone that interacts with steroid hormone receptors, including the glucocorticoid receptor (GR), the progesterone receptor, and the androgen receptor (O'Leary, 2013). It is one of the chaperones that maintains un-liganded GR in the cytoplasm, thus reducing the affinity of GR for cortisol and reducing translocation of GR to the nucleus. Proline cis-trans isomerization is important for proper protein folding, but deletion of the N-terminal PPIase domain had little effect on the efficacy of the FKBP5 protein as a chaperone. It appears that the binding activity of the FKBP5 protein may be more important than its PPIase enzymatic activity in terms of GR signaling (O'Leary, 2013).

[0034] FKBP5 gene expression is induced by glucocorticoids (including cortisol) as part of an intracellular ultrashort negative feedback loop for GR activity (Vermeer, 2003). This induction is mediated by GR (Vermeer, 2003; Caldwell 2010). Chronic administration of corticosterone to mice, also results in elevated FKBP5 gene expression (Lee, 2010; Ewald, 2014).

[0035] Overexpression of FKBP5 *in vitro* reduces glucocorticoid binding affinity and nuclear translocation of GR. Naturally occurring over-expression of FKBP5 causes GR resistance in New World monkeys (Scammell, 2001), which is accompanied by increased cortisol levels. A role for FKBP5 in bone destruction, the development of osteoporosis in rheumatoid arthritis, and in glucocorticoid induced osteoporosis has been suggested (Kimura, 2013). Overexpression of FKBP5 *in vivo* in a rTg45 10 tau transgenic mouse model resulted in an increase in the level of phosphorylated tau and was associated with neuronal loss (Blair, 2013). In humans, overexpression of FKBP5 has been associated with Alzheimer's disease (Blair, 2013).

[0036] Polymorphisms of FKBP5 have been linked with several diseases, including depression (Binder 2004), post-traumatic stress disorder (Binder 2008), mood disorders (Binder 2009) and bipolar disorder (Willour, 2009). FKBP5 polymorphisms have also been linked to the response to anti-depressant treatment (Binder, 2004).

[0037] Yang *et al* demonstrated that fasting induces FKBP5 gene expression in the hypothalamus in mice and rats. Overexpression of the FKBP5 gene in mice on a high fat diet resulted in persistent elevated body weight and impaired glucose tolerance, suggesting that elevated FKBP5 expression and/or elevated FKBP5 protein levels or activity promotes an obese phenotype.

[0038] A recent study by Pereira *et al* (Metabolism, 2014) demonstrates that the FKBP5 gene is regulated by dexamethasone in human subcutaneous and omental adipose tissue. FKBP5 is among the top genes stimulated by the GR agonist dexamethasone. The authors also report that FKBP5 expression in adipose tissue is correlated with markers of insulin resistance. In addition, SNPs in the FKBP5 region were associated with type 2 diabetes and diabetes-related traits.

a. Treatment of diseases with a glucocorticoid receptor antagonist (GRA)

[0039] The GR is involved in a wide variety of diseases or conditions. In some cases, antagonizing GR activity or signaling (*e.g.*, by administration of a glucocorticoid receptor antagonist (GRA)) can treat such diseases or conditions. However, there exists a great deal of variability in the susceptibility of certain diseases or conditions to treatment with a GRA. In some cases, the cells, tissue, or organ affected by the disease or condition can be, or can become, resistant to, or unaffected by, the administration of one or more GRAs. For example, although certain breast cancer cells (*e.g.*, triple negative breast cancer cells) can be responsive to GRA treatment (*e.g.*, in combination with one or more chemotherapeutics), not all such breast cancer cells are so responsive. Similarly, some diseases or conditions caused by or associated with elevated levels of cortisol exhibit variable treatment efficacy by administration of one or more GRAs. In some cases, identification of a clinical or biochemical response to the GRA can indicate that the GRA treatment should be continued. In some cases, a lack of a clinical or biochemical response can indicate that a different treatment (*e.g.*, administration of a different GRA or administration of the same GRA at a higher dose) is indicated. Such responsiveness can vary from subject to subject, cell to cell, tissue to tissue, or during the course of a subject's disease progression. Thus there is a need for alternative methods for assessing a clinical or biochemical response to a GRA in a human subject.

[0040] Accordingly, described herein are methods of detecting or assessing a clinical or a biochemical response to administration of a glucocorticoid receptor antagonist (GRA) for treatment of a disease or condition. The methods for detecting or assessing a clinical or biochemical response to a GRA described herein involve detection of: (i) the activity or amount of FKBP5 protein; or (ii) the expression level of a gene encoding the FKBP5 protein (*e.g.*, the absolute or relative amount of FKBP5 mRNA), in one or more provided samples from a human subject.

[0041] In some cases, the methods described herein involve detection of, or detection of a change in,: (i) the activity or amount of FKBP5 protein; or (ii) the expression level of a gene encoding the FKBP5 protein (*e.g.*, the absolute or relative amount of FKBP5 mRNA), in a subject. Such a change can be detected by determining the activity or amount of FKBP5 protein, or the expression level of a gene encoding FKBP5, in a first sample from a subject and comparing the results to the results from a second sample from the subject. The first sample can be provided or obtained from the subject prior to one or more steps of administering a GRA, and the second sample can be provided or obtained from the subject after one or more steps of administering a GRA.

b. Cushing's syndrome

[0042] Also described herein are methods of diagnosing Cushing's syndrome. Cushing's syndrome is a condition caused by the excessive production of the glucocorticoid cortisol by the adrenal cortex. The condition is often due to the presence of a tumor or hyperplasia that exhibits unregulated secretion of adrenocorticotropic hormone (ACTH). The unregulated secretion of ACTH in turn induces the adrenal glands to secrete excess cortisol. Cortisol generally participates in a negative feedback loop, in which high levels of cortisol suppress secretion of both ACTH and cortisol. However, in Cushing's syndrome, this negative regulation is not effective or absent, resulting in chronic hypercortisolemia.

[0043] Cushing's syndrome can be diagnosed in a variety of ways. One method of diagnosis is known as the dexamethasone suppression test (DST). In this test, the glucocorticoid receptor agonist dexamethasone is administered to a patient and cortisol levels are measured after administration. The agonist can be administered in a low dose (*e.g.*, 1-2 mg) to measure effects of a low dose on cortisol levels. In some cases, a high dose is also administered (*e.g.*, 8 mg) to measure the effects of a high dose on cortisol levels. Moreover, ACTH levels can be determined prior to administration of dexamethasone for additional information. The presence of a low ACTH level and a cortisol level that is not suppressed by high or low dose dexamethasone indicates primary hypercortisolemia caused by, *e.g.*, cortisol secreting adenoma tumors in the adrenal cortex. This type of Cushing's syndrome is not typically subject to ACTH or cortisol regulation.

[0044] The cortisol cut off for the DST has been a moving target. Currently the endocrine society recommends a cut off of 1.8 μg/dl and, the AACE guidelines recently decreased the cut off to 3 μg/dl (previously it was higher at 5 μg/dl). Endocrine societies in other countries

use different cut offs. Thus, there is no general consensus of the most appropriate cut off to use. Moreover, the DST has high sensitivity but low specificity, therefore current guidelines for the diagnosis of Cushing's syndrome (CS) require at least 2 confirmatory tests (*e.g.*, a DST and confirmation by an alternative diagnostic method).

[0045] In addition, the false positive rate of the 1 mg DST is high in certain populations (severe insulin resistance, fatty liver disease, PCOS *etc.*, *see* "The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline (2008), published as J. Clin. Endocrin. & Metab., May 2008, 93(5):1526-40.). Also medications that affect the metabolism of dexamethasone can influence the test (see guidelines from the Endocrine Society). Another important limitation for the 1 mg DST is the fact that 10-15 % of confirmed Cushing's disease (CD) cases drop below the 2 μg/dl cut off with the 1 mg DST (Findling *et al.*, J. Clin. Endocrinol. Met., 2004, 89:1222-1226) and thus would not be diagnosed by this test. Moreover, there is no consensus about the best diagnostic criterion for milder forms of Cushing's, especially adrenal Cushing's (see Endocrine Society guidelines, under adrenal incidentalomas).

[0046] An alternative to the dexamethasone suppression test (DST) is the 24 hours urine free cortisol (UFC) test. However, the UFC test has very low sensitivity in mild forms of CS. In addition the quality of the current assays is poor (see Raff *et al.* J. Clin. Endocrinol. Met., 2015, 100:395-397). It is a useful test for overt cases of CS, but there are often false negative results even in full blown cases, which can complicate the diagnostic process and delay the diagnosis. In addition, in cases of cyclical CS the diagnosis of CS can be missed if the test is done when the tumor is less active.

[0047] Another alternative to the DST is based on midnight salivary cortisol levels. This test also is less sensitive in milder forms of CS. It can be useful to diagnose early relapse of CD after transsphenoidal surgery. However, it has a lot of false positives and false negatives. It depends on whether the patient is able to perform the test properly, and inappropriate sample collection is frequently a confounding factor.

[0048] It is also possible to distinguish between Cushing's disease and Cushing's syndrome by administration of desmopressin or CRH. CRH can be useful in the differential diagnosis of Cushing's syndrome, because most patients with Cushing's disease respond to CRH, while those with other types of Cushing's syndrome generally do not. Although these tests, and in particular the dexamethasone suppression test, are widely used to diagnose Cushing

syndrome and/or distinguish between Cushing's disease and other types of Cushing's syndrome, they are not definitive, and can yield an undesirable number of false positives and false negatives.

[0049] Accordingly, the present inventors have developed an improved method for diagnosing Cushing's syndrome. The method can include detecting: (i) the activity or amount of FKBP5 protein; or (ii) the expression level of a gene encoding the FKBP5 protein, in one or more samples from a human subject.

II. Methods

a. Assessing a clinical or a biochemical response to a GRA or to a medical or surgical therapy for treatment of hypercortisolemia

[0050] Described herein is a method for assessing a clinical or a biochemical response to a glucocorticoid receptor antagonist (GRA) in a human subject. The method can be useful, *e.g.*, for confirming the efficacy of a treatment modality, monitoring treatment outcomes, or guiding treatment decisions. For example, if a patient presents with a disease or condition known to be, or suspected of being, treatable with a GRA, then a GRA can be administered, and the clinical response to the GRA can be assessed using one or more of the methods described herein. In some cases, a positive indication of a clinical or biochemical response, or an indication of a strong clinical or biochemical response, to the GRA can then predict a positive clinical outcome, an increased likelihood of a positive clinical outcome, or suggest continuation of GRA administration. In some cases, a negative indication of a clinical or biochemical response, or a lack of a strong clinical or biochemical response, can predict a negative clinical outcome, an increased likelihood of a negative clinical outcome, or suggest administration of an increased dose of the GRA or administration of an alternative GRA. In some cases, a negative indication of a clinical response or a biochemical response, or a lack of a strong clinical or biochemical response, can suggest a need for additional or alternative treatments.

[0051] The method for assessing a clinical or biochemical response to a glucocorticoid receptor antagonist (GRA) in a human subject can include: a) measuring a first amount, or activity of FKBP5 protein or a first expression level of a gene encoding FKBP5 protein in a first sample from the subject, wherein i) the first sample comprises primary cells; and ii) the first sample is obtained before administering the GRA to the subject; b) optionally administering the GRA to the subject; c) measuring a second amount or activity of FKBP5

protein or a second expression level of a gene encoding FKBP5 protein in a second sample from the subject, wherein: i) the second sample comprises primary cells; and ii) the second sample is obtained after administering the GRA to the subject; and d) comparing the first and second amounts, activities, or expression levels, wherein a reduction in the amount or activity of FKBP5 protein or a reduction in the expression level of the gene encoding FKBP5 protein in the second sample indicates the response to the GRA.

[0052] In some cases, the subject has received one or more doses of a GRA prior to the obtaining of a first sample. For example, the subject may be undergoing GRA therapy, or may have previously undergone GRA therapy. Thus, in some cases, the pre-GRA administration sample may be obtained a suitable period of time after a GRA administration to allow for measurement of baseline FKBP5 levels that are unaffected by the presence of a GRA. Thus, in some cases, the first sample, which is obtained prior to administering the GRA to the subject, is obtained at least 4, 5, 6, 7, 8, 9, 10, 12, 16, 18, or 24 hours after a previous GRA administration, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or 31 days after a previous GRA administration. A suitable period of time between a previous administration of a GRA and obtaining a first sample can be determined based on the pharmacokinetics of a previously administered GRA. In some cases, a suitable period of time is a length of time sufficient for the GRA to be completely removed from the subject. In some cases, a suitable period of time is a length of time sufficient for the GRA to have no or minimal effect on FKBP5 levels (*e.g.*, amount or activity of FKBP5 protein or mRNA levels).

[0053] In some cases, the subject is administered multiple doses of a GRA between the obtaining of the first sample and the obtaining of the second sample. In some cases, the subject is administered, or is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or more doses between the obtaining of the first sample and the obtaining of the second sample. In some cases, the subject is administered a GRA, and the second sample is obtained after a period of time suitable to allow for downregulation of FKBP5. For example, the second sample can be obtained at least 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours after GRA administration. In other cases, the second sample can be obtained between doses of a multiple GRA dosage schedule. In yet other cases, the second sample is obtained immediately prior, immediately after, or during one or more GRA administrations. In any case, the second sample is obtained after at least one dose of GRA has been administered to the subject.

[0054] Also described herein is a method for assessing a clinical or a biochemical response in a human subject to administering to the subject a medical or surgical therapy for treatment of hypercortisolemia. The method can be useful, *e.g.*, for confirming the efficacy of a treatment modality, monitoring treatment outcomes, or guiding treatment decisions. For example, if a patient presents with hypercortisolemia, then a medical or surgical therapy can be administered, and the clinical response to the medical or surgical therapy can be assessed using one or more of the methods described herein. In some cases, a positive indication of a clinical or biochemical response, or an indication of a strong clinical or biochemical response, to the medical or surgical therapy can then predict a positive clinical outcome, an increased likelihood of a positive clinical outcome, or suggest continuation of the medical or surgical therapy. In some cases, a negative indication of a clinical or biochemical response, or a lack of a strong clinical or biochemical response, can predict a negative clinical outcome, an increased likelihood of a negative clinical outcome, or suggest administration of an increased dose or additional doses of a medical therapy, or administration of an alternative medical or surgical therapy. In some cases, a negative indication of a clinical response or a biochemical response, or a lack of a strong clinical or biochemical response, can suggest a need for additional or alternative treatments.

[0055] The method for assessing a clinical or biochemical response to a medical or surgical therapy for hypercortisolemia in a human subject can include: a) measuring a first amount, or activity of FKBP5 protein or a first expression level of a gene encoding FKBP5 protein in a first sample from the subject, wherein i) the first sample comprises primary cells; and ii) the first sample is obtained before administering the medical or surgical therapy to the subject; b) optionally administering the medical or surgical therapy to the subject; c) measuring a second amount or activity of FKBP5 protein or a second expression level of a gene encoding FKBP5 protein in a second sample from the subject, wherein: i) the second sample comprises primary cells; and ii) the second sample is obtained after administering the medical or surgical therapy to the subject; and d) comparing the first and second amounts, activities, or expression levels, wherein a reduction in the amount or activity of FKBP5 protein or a reduction in the expression level of the gene encoding FKBP5 protein in the second sample indicates the response to the medical or surgical therapy for treatment of hypercortisolemia.

[0056] In some cases, the medical or surgical therapy includes administering an inhibitor of steroidogenesis. Exemplary inhibitors of steroidogenesis include, but are not limited to, aminoglutethimide, cholesterol sulfate, ketoconazole, levoketoconazole, metyrapone,

LCI699, mitotane, and etomidate. In some cases, the medical or surgical therapy includes administering an ACTH modulator. Exemplary ACTH modulators include, but are not limited to, dopamine agonists, retinoic acid, R-roscovitine, somatostatin, and somatostatin analogues. Exemplary dopamine agonists include, but are not limited to, bromocriptine, and cabergoline. Exemplary somatostatin analogues include, but are not limited to, pasireotide, octreotide, and lanreotide. In some cases, the medical or surgical therapy is or includes GRA administration. In some cases, the medical or surgical therapy is or includes transsphenoidal surgery, or repeat transsphenoidal surgery. In some cases, the medical or surgical therapy is or includes adrenalectomy, unilateral adrenalectomy, or bilateral adrenalectomy. In some cases, the medical or surgical therapy is or includes radiotherapy. In some cases, the medical or surgical therapy is or includes resection of a non-pituitary ACTH-secreting tumor. In some cases, the medical or surgical therapy is or includes treatment with a peptide receptor radionuclide therapy (*e.g.*, Y-90 or Lu-177 labeled octreotide). In some cases, the medical or surgical therapy is or includes a combination of any two or more of the foregoing medical or surgical therapies. In some cases, the combination is a combination of two or more medical therapies. In some cases, the combination is a combination of two or more surgical therapies. In some cases, the combination is a combination of a medical therapy and a surgical therapy.

[0057] In some cases, the subject has received one or more doses of a medical therapy for hypercortisolemia prior to the obtaining of a first sample. For example, the subject may be undergoing GRA therapy, or may have previously undergone GRA therapy. Thus, in some cases, the pre-medical therapy administration sample may be obtained a suitable period of time after a medical therapy administration to allow for measurement of baseline FKBP5 levels that are unaffected by the presence of the medical therapy. Thus, in some cases, the first sample, which is obtained prior to administering the medical therapy to the subject, is obtained at least 4, 5, 6, 7, 8, 9, 10, 12, 16, 18, or 24 hours after a previous medical therapy administration, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or 31 days after a previous medical therapy administration. A suitable period of time between a previous administration of a medical therapy and obtaining a first sample can be determined based on the pharmacokinetics of a previously administered medical therapy. In some cases, a suitable period of time is a length of time sufficient for the medical therapy to be completely removed from the subject. In some cases, a suitable period of time is a length of time sufficient for the medical therapy to have no or minimal effect on FKBP5 levels (*e.g.*, amount or activity of FKBP5 protein or mRNA levels).

[0058] In some cases, the subject is administered multiple doses of a medical therapy between the obtaining of the first sample and the obtaining of the second sample. In some cases, the subject is administered, or is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or more doses between the obtaining of the first sample and the obtaining of the second sample. In some cases, the subject is administered a medical therapy, and the second sample is obtained after a period of time suitable to allow for downregulation of FKBP5 expression, amount, or activity. For example, the second sample can be obtained at least 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours after administration of the medical therapy. In other cases, the second sample can be obtained between doses of a multiple dosage schedule. In yet other cases, the second sample is obtained immediately prior, immediately after, or during one or more administrations of a medical therapy. In any case, the second sample is obtained after at least one dose of a medical therapy has been administered to the subject.

i. Sample extraction, preparation, and analysis

[0059] The sample can be obtained by any means known in the art. For example, the sample can be obtained by collecting a blood sample (*e.g.*, a sample of whole blood or a fraction thereof). Alternatively, the sample can be obtained by scraping epithelial cells (*e.g.*, nasal epithelial cells) of a subject. Samples include, but are not limited to samples of human cells and tissues, such as blood samples, cerebrospinal fluid samples, synovial tissue samples, synovial fluid samples, brain tissue samples, blood vessel samples, or tumor samples.

[0060] Samples encompass samples of healthy or pathological cells, tissues or structures. In some cases, the sample can be provided by obtaining cells of a tissue or organ affected by a disease or condition mediated by GR activity or signaling. For example, in human subjects suffering from a type of cancer that can be treated with a GRA (*e.g.*, a GRA in combination with a chemotherapeutic), a sample containing primary tumor cells can be obtained and assayed as described herein. Such cancers include, but are not limited to, breast cancer, triple negative breast cancer, prostate cancer, metastatic prostate cancer, androgen resistant prostate cancer, and ovarian cancer. In some cases, the sample can be provided by obtaining cells of a subject suffering from hypercortisolemia. In some cases, the sample can be provided by obtaining cells of a tissue or organ affected by hypercortisolemia. In some cases, the sample can be provided by obtaining cells of a subject suffering from or suspected of being suffering from Cushing's syndrome. In some cases, the sample can be provided by obtaining cells of a tissue or organ affected by, or suspected of being affected by, Cushing's syndrome.

[0061] The sample can be extracted to obtain FKBP5 protein, or FKBP5 nucleic acid. For example, cells can be lysed, and the protein fraction obtained. In some cases, the lysate is further fractionated to purify a specified cellular compartment. For example, the cell lysate can be fractionated to obtain a cytosolic protein fraction. As another example, the cell lysate can be fractionated to obtain a nuclear or nucleolar protein fraction. The protein fraction can be assayed for FKBP5 protein levels or activity. Alternatively, the cells can be lysed, and a nucleic acid (*e.g.*, mRNA) fraction obtained. The nucleic acid fraction can be assayed for expression of the gene encoding FKBP5. For example, the expression can be assayed by quantitative amplification (*e.g.*, qPCR), or reverse transcription and subsequent quantitative amplification (*e.g.*, RT-qPCR).

[0062] The cell lysate, or protein fraction thereof, can be purified using a variety of methods to obtain a fraction enriched for FKBP5 protein, or a portion thereof. For example, cells can be lysed and contacted with a chromatography medium under conditions suitable to preferentially bind contaminants or target protein. Where contaminants are preferentially bound, target protein can be collected as a flow through fraction and assayed further. Where target protein is bound, the chromatography medium can be washed and the target protein eluted.

[0063] As another example, cells can be lysed and contacted with a capture reagent (*e.g.*, a capture antibody or aptamer) that specifically binds to the FKBP5 protein, or a portion thereof. The capture reagent can be immobilized on a solid support. In some cases, the FKBP5 protein or portion thereof can be eluted from the capture reagent and then detected or quantified. In other cases, the FKBP5 protein or portion thereof can be detected or quantified as a capture reagent-bound form.

[0064] Similarly, the cell lysate, or nucleic acid fraction thereof can be purified using a variety of methods to obtain a fraction enriched for a transcript of a gene encoding FKBP5. For example, cells can be lysed and nucleic acids can be precipitated or otherwise purified from the lysate. In some cases, the nucleic acids can be purified by contacting the sample, or a fraction thereof, with a surface immobilized oligodT moiety to preferentially bind polyadenylated mRNA.

[0065] Nucleic acids can be subject to amplification, hybridization, polymerization, reverse transcription, or a combination thereof. In some cases, the amplification, hybridization, polymerization, or reverse transcription is target specific such that the gene encoding FKBP5,

a transcript thereof, or a portion thereof is specifically amplified, hybridized, or reverse transcribed. In some cases, the amplification, hybridization, polymerization, or reverse transcription is not target specific such that the sample is subject to whole genome or whole transcriptome hybridization, polymerization, or reverse transcription. Whole genome or other non-specific hybridization, polymerization, or reverse transcription can be performed with the use of one or more degenerate primers or probes. After non-specific hybridization, polymerization, or reverse transcription, the gene encoding FKBP5 can be detected and/or quantified.

[0066] The amount or activity of FKBP5 polypeptide, or a portion thereof, can be measured by a variety of methods known in the art. For example, an ELISA (*e.g.*, sandwich ELISA) can be used to measure polypeptide levels in a sample, or a protein extract thereof, using one or more antibodies specific for the FKBP5 protein, or a portion thereof. In some cases, the ELISA is a sandwich ELISA, in which FKBP5 polypeptide, or a portion thereof, is immobilized by binding to an immobilized capture reagent (*e.g.*, capture antibody or aptamer), and the immobilized polypeptide or portion thereof is detected with a detection reagent (*e.g.*, detection antibody or aptamer).

[0067] As another example, activity of the FKBP5 polypeptide, or a portion thereof, can be measured by contacting the sample, or a protein extract thereof, with a proline containing peptide substrate to measure the FKBP5-mediated cis-trans prolyl isomerase activity of the sample. In some cases, the isomerization of the substrate can be measured using an cis-trans proline isomer sensitive enzyme, such as a protease. For example chymotrypsin, which has a high substrate specificity and catalytic efficiency (k_{cat}/Km) against peptide substrates having a trans-proline at the P2 position and phenylalanine or tyrosine at the P1 position, but very little or no specificity or catalytic efficiency against such peptides containing a cis-proline at P2, can be used to measure prolyl isomerase activity. For instance, an N-succinyl-Ala-Leu-*cis*-Pro-Phe-*p*-nitroanilide substrate can be used in combination with chymotrypsin, which preferably cleaves the trans prolyl isomer of the substrate to assay a sample or extract thereof for FKBP5 prolyl isomerase activity. The production of the trans isomer of the substrate by isomerase activity of the FKBP5 or portion thereof can be measured by detecting the digestion of the nitroanilide substrate by the chymotrypsin as described, *e.g.*, in Fischer *et al.* Nature. 1989 Feb 2;337(6206):476-8.

[0068] As another example, activity of the FKBP5 polypeptide, or a portion thereof, can be detected or quantified by measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample. This can be performed, *e.g.*, by purifying GR or FKBP5 protein under conditions suitable to preserve binding between GR and FKBP5 protein. The purification product can then be assayed for the presence, absence, or quantity of the cognate binding partner. For example, cytosolic GR can be purified and the presence of FKBP5 protein detected in the purification product. As another example, FKBP5 protein can be purified and the presence of GR can be detected in the purification product. In some cases, this can be performed using a sandwich ELISA-type assay in which the immobilized capture reagent recognizes one member of the GR:FKBP5 protein complex and the detection reagent recognizes the other member of the GR:FKBP5 protein complex.

[0069] As another example, expression of a gene encoding FKBP5 can be measured by reverse transcription of FKBP5 mRNA, or a portion thereof, and quantitative amplification of the reverse transcription product or a portion thereof. The quantitative amplification can be performed using PCR (*e.g.*, real time PCR) or other amplification techniques known in the art. The amplification can be detected by, *e.g.*, detecting incorporation of an intercalating dye into the amplification product, degradation of a quenched fluorescence hydrolysis probe, or binding of quenched molecular beacon.

[0070] Any measured amount or activity or expression level in a sample can be normalized to a reference. For example, an expression level can be normalized to the amount of total mRNA, or the expression level of a reference gene. Suitable reference genes include, but are not limited to, GAPDH, hypoxanthine phosphoribosyltransferase 1 (HRPT1), ribosomal protein large P1, or another housekeeping gene. As another example, FKBP5 protein amount can be normalized to total protein levels, or the level of a reference gene product. Suitable reference gene products include, but are not limited to, actin, tubulin, COX IV, HRPT1, GAPDH, or another housekeeping gene product.

ii. Comparing FKBP5 amount activity or expression

[0071] In some embodiments, the amount or activity of FKBP5 or the expression level of a gene encoding FKBP5 protein after administration of a GRA is quantified from a sample obtained after administration of one or more doses of the GRA and compared to a control or threshold value rather than a pre-GRA administration value. In some cases, the control or threshold value is a positive control or threshold value that indicates a biochemical or clinical

response, or a strong biochemical or clinical response to the GRA in the tissue, organ, or cell-type subject to the assay. Thus in such cases, a quantified amount, activity, or expression level that is near, equal to, or below the positive control or threshold value can indicate a biochemical or clinical response or a strong biochemical or clinical response to the GRA. In contrast, a quantified amount, activity, or expression level that is above, or significantly above, the positive control or threshold value can indicate a lack of a biochemical or clinical response, or a lack of a strong biochemical or clinical response to the GRA.

[0072] In some cases, the quantified amount, activity, expression that indicates a biochemical or clinical response to the GRA is equal to about, or less than about, 25%, 30%, 40%, 50%, 75%, 100%, 110%, 125%, or 150% of the positive control or threshold value. In some cases, the quantified amount, activity, or expression that indicates a lack of a biochemical or clinical response to the GRA is equal to about or above about a 2-fold, 2.5-fold, 3-fold, 4-fold, 5-fold, 7.5-fold, 10-fold, 12-fold, 15-fold, 20-fold, 25-fold, 30-fold, 40-fold, or 50-fold multiple of the positive control or threshold value.

[0073] In some cases, the control or threshold value is a negative control or threshold value that indicates a lack of a response (*e.g.*, biochemical or clinical) to a GRA or a value that is typically obtained without, or prior to, administration of a GRA. Thus in such cases, a quantified amount, activity, or expression level that is below the negative control or threshold value (*e.g.*, significantly below) can indicate a clinical or biochemical response or a strong clinical or biochemical response to the GRA. In contrast, a quantified amount, activity, or expression level that is near, equal to, or above the negative control or threshold value can indicate a lack of a clinical response, a lack of biochemical response, a lack of a strong clinical response, or a lack of a strong biochemical response to the GRA. In some cases, the quantified amount, activity, or expression that indicates a clinical response to the GRA or a biochemical response to the GRA is equal to about or less than about 0.25%, 0.5%, 1%, 5%, 7.5%, 10%, 12.5%, 15%, 17.5%, 20%, 25%, 30%, 40%, or 50% of the negative control or threshold value. In some cases, the quantified amount, activity, or expression that indicates a lack of a clinical response or a lack of a biochemical response to the GRA is at least about 75%, 100%, 110%, 125%, 150%, 200%, 300%, or 400% of the negative control or threshold value.

[0074] In some embodiments, the amount or activity of FKBP5 protein or the expression level of a gene encoding FKBP5 after administration of a GRA is quantified from a sample

obtained after administration of one or more doses of the GRA and compared to a value quantified from a sample obtained prior to administration of one or more doses of the GRA. A quantified post-administration amount activity or expression level that is below the pre-administration value can indicate a clinical response, a biochemical response, a strong clinical response, or a strong biochemical response to the GRA. In contrast, a quantified post-administration amount activity or expression level that is near or equal to the pre-administration value can indicate a lack of a clinical response, a lack of a biochemical response, a lack of a strong biochemical response, or a lack of a strong clinical response to the GRA. In some cases, when the post-GRA administration value is greater than the pre-GRA administration value, progression of the disease or condition in the human subject is indicated. In some cases, when the post-GRA administration value is less than the pre-GRA administration value, improvement of the disease or condition in the human subject is indicated.

[0075] The provided pre-GRA administration sample can be taken at any time prior to administration of a GRA, including but not limited to, immediately before GRA administration; at least about 1, 2, 3, 4, 6, 7, 8, 10, 15, 20, 25, 30, 45, 50, 60, 80, or 90 minutes before GRA administration; at least about 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, or 22 hours before GRA administration; at least about 1, 2, 3, 4, 5, or 6 days before GRA administration; or at least about 1, 1.5, 2, 3, or 4 weeks before GRA administration. In some cases, the provided pre-administration sample is obtained from about 0 to about 12, from about 0 to 6 hours, from about 0 to about 4 hours, from about 1 to 4 hours, or from about 2 to 6 hours prior to administration of the GRA.

[0076] The provided post-GRA administration sample can be taken after a time suitable to allow the activity of the GRA to manifest in a change (*e.g.*, a detectable change) in FKBP5 amount or activity, or a change in expression of a gene encoding FKBP5. In some cases, the time is selected to achieve a maximum possible response (*e.g.*, clinical or biochemical response) to GRA administration. In some cases, the delay between administration of the GRA and obtaining of the post-GRA administration sample is at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 20, 25, 30, 40, or 50 minutes; 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 15, 16, 18, 20, or 22 hours; 1, 2, 3, 4, 5, or 6 days; or 1, 2, 3, or 4 weeks.

[0077] The provided post-GRA administration sample can be taken after multiple administrations of one or more GRAs. For example, one or more GRAs can be administered

to a human subject in need thereof for a period of days (*e.g.*, 1, 2, 3, 4, 5, or 6 days) or weeks (*e.g.*, 1, 2, 3, 4, or 5 weeks) and then a post-administration sample obtained and analyzed for FKBP5 protein amount or activity or FKBP5 gene expression to assess a clinical response to the GRA or to assess a biochemical response to the GRA.

[0078] In some cases, the quantified post-GRA administration amount, activity, or expression that indicates a clinical or biochemical response to the GRA is less than about, 300%, 250%, 200%, 150%, 100%, 75%, 50%, 40%, 30%, 25%, 20%, 15%, 10%, 7.5%, 5%, 2.5%, 2%, 1.5%, or 1% of the pre-GRA administration value. In some cases, the quantified post-GRA administration amount activity or expression that indicates a lack of a clinical or biochemical response to the GRA is equal to about or above about 75%, 80%, 85%, 90%, 100%, 110%, 120%, 125%, 150%, or 200% of the pre-GRA administration value.

[0079] In some cases, the human subject can have cancer, and methods described herein can be employed to assess or predict the effect of GRA therapy on the cancer cells of the subject. In some cases, cancer cells are obtained from a subject and assayed for FKBP5 amount or activity or the expression level of a gene encoding FKBP5. In some cases, a high level of FKBP5 relative to a control may suggest that the cells express a high level of GR and GRA therapy may be indicated. In some cases, a low level of FKBP5 relative to a control may suggest that the cells express a low level of GR and GRA therapy is not indicated. In some cases, a low level of FKBP5 relative to a control may suggest that the FKBP5 feedback mechanism is inoperative, and thus GRA therapy may be indicated. In some cases, a reduction in FKBP5 in tumor cells after administration of GRA as compared to a pre-administration value can suggest that GRA therapy is indicated.

[0080] Similarly, FKBP5 amount, activity, or expression level can be assessed in combination with GR amount, activity, or expression level. In some cases, low GR amount, activity, or expression level and low FKBP5 amount, activity, or expression level can predict that GRA therapy is not beneficial for this cancer type, cell, or tumor. In some cases, high GR amount, activity, or expression level and high FKBP5 amount, activity, or expression level can indicate that GRA therapy can be beneficial for this cancer type, cell, or tumor. In some cases, high GR amount, activity, or expression level and low FKBP5 amount, activity, or expression level can indicate a defective cortisol counter regulation mechanism and GRA therapy can be a beneficial treatment.

[0081] In some cases, FKBP5 levels can be detected in tumor cells that have been extracted from a patient and cultured *in vitro*. For example, a sample containing tumor cells can be obtained, a portion of the sample assayed for FKBP5 (protein or expression), and a GRA administered to a different portion of the sample. The GRA administered sample can be assayed for FKBP5 protein amount, or activity, or FKBP5 gene expression and compared to the pre-administration value.

[0082] In some cases, FKBP5 levels can be determined after transsphenoidal surgery to detect relapse or remission of Cushing's syndrome. For example, FKBP5 can be measured in samples obtained before and after transsphenoidal surgery. Additionally or alternatively, FKBP5 can be detected in samples obtained at several time points after transsphenoidal surgery. For example, FKBP5 can be detected in one or more samples obtained within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13,14, 15, 16, 17, 18, 19, or 20 days after transsphenoidal surgery. In some cases, a low level of FKBP5 relative to a control can indicate that the subject is exhibiting remission of Cushing's syndrome or is not exhibiting early relapse of Cushing's syndrome. In some cases, a decrease in FKBP5 as compared to the value detected in a sample obtained prior to transsphenoidal surgery indicates that the subject is exhibiting remission of Cushing's syndrome or is not exhibiting early relapse of Cushing's syndrome. In some cases, a stable or decreasing value of FKBP5 in samples taken at multiple time points after transsphenoidal surgery indicates that the subject is exhibiting remission of Cushing's syndrome or is not exhibiting early relapse of Cushing's syndrome.

[0083] In some embodiments, in the absence of a detected reduction in the amount or activity of FKBP5 protein or expression of the gene encoding FKBP5 protein after administration of the GRA and relative to a pre-GRA administration or control value, the method comprises administering an increased amount of GRA to the subject, or administering an alternative GRA to the subject, or a combination thereof. In some embodiments, in the absence of a detected reduction that is greater than a threshold value in the amount or activity of FKBP5 protein or expression of the gene encoding FKBP5 protein after administration of the GRA and relative to a pre-GRA administration or control value, the method comprises administering an increased amount of GRA to the subject, or administering an alternative GRA to the subject, or a combination thereof.

[0084] In some embodiments, the amount or activity of FKBP5 or the expression level of a gene encoding FKBP5 protein after administration of a medical (*e.g.*, GRA) or surgical

therapy for treatment of hypercortisolemia is quantified from a provided sample obtained after administration of one or more doses of a medical therapy for treatment of hypercortisolemia and compared to a control or threshold value rather than a pre-administration value. In some cases, the control or threshold value is a positive control or threshold value that indicates a biochemical or clinical response, or a strong biochemical or clinical response to the medical or surgical therapy in the tissue, organ, or cell-type subject to the assay. Thus in such cases, a quantified amount, activity, or expression level that is near, equal to, or below the positive control or threshold value can indicate a biochemical or clinical response or a strong biochemical or clinical response to the medical or surgical therapy for treatment of hypercortisolemia. In contrast, a quantified amount, activity, or expression level that is above, or significantly above, the positive control or threshold value can indicate a lack of a biochemical or clinical response, or a lack of a strong biochemical or clinical response to the medical or surgical therapy for treatment of hypercortisolemia.

[0085] In some cases, the quantified amount, activity, expression that indicates a biochemical or clinical response to the medical or surgical therapy for treatment of hypercortisolemia is equal to, about, or less than about, 25%, 30%, 40%, 50%, 75%, 100%, 110%, 125%, or 150% of the positive control or threshold value. In some cases, the quantified amount, activity, or expression that indicates a lack of a biochemical or clinical response to the medical or surgical therapy for treatment of hypercortisolemia is equal to, about, or above about a 2-fold, 2.5-fold, 3-fold, 4-fold, 5-fold, 7.5-fold, 10-fold, 12-fold, 15-fold, 20-fold, 25-fold, 30-fold, 40-fold, or 50-fold multiple of the positive control or threshold value.

[0086] In some cases, the control or threshold value is a negative control or threshold value that indicates a lack of a response (*e.g.*, biochemical or clinical) to a medical or surgical therapy for treatment of hypercortisolemia or a value that is typically obtained without, or prior to, administration of a medical or surgical therapy for treatment of hypercortisolemia. Thus in such cases, a quantified amount, activity, or expression level that is below the negative control or threshold value (*e.g.*, significantly below) can indicate a clinical or biochemical response or a strong clinical or biochemical response to the medical or surgical therapy for treatment of hypercortisolemia. In contrast, a quantified amount, activity, or expression level that is near, equal to, or above the negative control or threshold value can indicate a lack of a clinical response, a lack of biochemical response, a lack of a strong clinical response, or a lack of a strong biochemical response to the medical or surgical

therapy for treatment of hypercortisolemia. In some cases, the quantified amount, activity, or expression that indicates a clinical response to the medical or surgical therapy for treatment of hypercortisolemia or a biochemical response to the medical or surgical therapy for treatment of hypercortisolemia is equal to, about, or less than about 0.25%, 0.5%, 1%, 5%, 7.5%, 10%, 12.5%, 15%, 17.5%, 20%, 25%, 30%, 40%, or 50% of the negative control or threshold value. In some cases, the quantified amount, activity, or expression that indicates a lack of a clinical response or a lack of a biochemical response to the medical or surgical therapy for treatment of hypercortisolemia is at least about 75%, 100%, 110%, 125%, 150%, 200%, 300%, or 400% of the negative control or threshold value.

[0087] In some embodiments, the amount or activity of FKBP5 protein or the expression level of a gene encoding FKBP5 after administration of a medical therapy for treatment of hypercortisolemia is quantified from a sample obtained after administration of one or more doses of the medical therapy for treatment of hypercortisolemia and compared to a value quantified from a sample obtained prior to administration of one or more doses of the medical therapy for treatment of hypercortisolemia. A quantified post-administration amount activity or expression level that is below the pre-administration value can indicate a clinical response, a biochemical response, a strong clinical response, or a strong biochemical response to the medical therapy for treatment of hypercortisolemia. In contrast, a quantified post-administration amount activity or expression level that is near or equal to the pre-administration value can indicate a lack of a clinical response, a lack of a biochemical response, a lack of a strong biochemical response, or a lack of a strong clinical response to the medical therapy for treatment of hypercortisolemia. In some cases, when the post-administration value is greater than the pre-administration value, progression of the hypercortisolemia condition in the human subject is indicated. In some cases, when the post-administration value is less than the pre-administration value, improvement of the hypercortisolemia condition in the human subject is indicated.

[0088] The pre-administration sample can be taken at any time prior to administration of a medical or surgical therapy for treatment of hypercortisolemia, including but not limited to, immediately before therapy administration; at least about 1, 2, 3, 4, 6, 7, 8, 10, 15, 20, 25, 30, 45, 50, 60, 80, or 90 minutes before therapy administration; at least about 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, or 22 hours before therapy administration; at least about 1, 2, 3, 4, 5, or 6 days before therapy administration; or at least about 1, 1.5, 2, 3, or 4 weeks before therapy administration. In some cases, the pre-administration sample is obtained from about 0 to

about 12, from about 0 to 6 hours, from about 0 to about 4 hours, from about 1 to 4 hours, or from about 2 to 6 hours prior to administration of the therapy.

[0089] The post-therapy administration sample can be taken after a time suitable to allow the activity of the therapy to manifest in a change (*e.g.*, a detectable change) in FKBP5 amount or activity, or a change in expression of a gene encoding FKBP5. In some cases, the time is selected to achieve a maximum possible response (*e.g.*, clinical or biochemical response) to therapy administration. In some cases, the delay between administration of the therapy and obtaining of the post-therapy administration sample is at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 20, 25, 30, 40, or 50 minutes; or 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 15, 16, 18, 20, 22, or 24 hours.

[0090] The post-therapy administration sample can be taken after multiple administrations of one or more medical or surgical therapies. For example, one or more medical therapies (*e.g.*, administration of a GRA, ACTH-modulator, inhibitor of steroidogenesis, *etc.*) can be administered to a human subject in need thereof for a period of days (*e.g.*, 1, 2, 3, 4, 5, or 6 days) or weeks (*e.g.*, 1, 2, 3, 4, or 5 weeks) and then a post-administration sample obtained and analyzed for FKBP5 protein amount or activity or FKBP5 gene expression to assess a clinical response to the medical therapy or to assess a biochemical response to the medical therapy. As another example, one or more surgical therapies (*e.g.*, transsphenoidal surgery, resection of a non-pituitary ACTH-secreting tumor, *etc.*) can be administered to a human subject in need thereof and then repeated, and then a post-administration sample obtained and analyzed for FKBP5 protein amount or activity or FKBP5 gene expression to assess a clinical response to the surgical therapy or to assess a biochemical response to the surgical therapy.

[0091] In some cases, the quantified post-administration amount, activity, or expression that indicates a clinical or biochemical response to the therapy is less than about, 75%, 50%, 40%, 30%, 25%, 20%, 15%, 10%, 7.5%, 5%, 2.5%, 2%, 1.5%, or 1% of the pre-administration value. In some cases, the quantified post-administration amount activity or expression that indicates a lack of a clinical or biochemical response to the therapy is equal to, about, or above about 80%, 85%, 90%, 100%, 110%, 120%, 125%, 150%, or 200% of the pre-administration value.

[0092] In some cases, FKBP5 levels can be determined after transsphenoidal surgery to detect relapse or remission of hypercortisolemia. For example, FKBP5 can be measured in samples obtained before and after transsphenoidal surgery. Additionally or alternatively,

FKBP5 can be detected in samples obtained at several time points after transsphenoidal surgery. For example, FKBP5 can be detected in one or more samples obtained within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13,14, 15, 16, 17, 18, 19, or 20 days after transsphenoidal surgery. In some cases, a low level of FKBP5 relative to a control can indicate that the subject is exhibiting remission of hypercortisolemia or is not exhibiting early relapse of hypercortisolemia. In some cases, a decrease in FKBP5 as compared to the value detected in a sample obtained prior to transsphenoidal surgery indicates that the subject is exhibiting remission of hypercortisolemia or is not exhibiting early relapse of hypercortisolemia. In some cases, a stable or decreasing value of FKBP5 in samples taken at multiple time points after transsphenoidal surgery indicates that the subject is exhibiting remission of hypercortisolemia or is not exhibiting early relapse of hypercortisolemia.

[0093] In some embodiments, in the absence of a detected reduction in the amount or activity of FKBP5 protein or expression of the gene encoding FKBP5 protein after administration of the medical or surgical therapy for treatment of hypercortisolemia and relative to a pre-administration or control value, the method comprises administering an increased amount of a medical therapy to the subject, administering an alternative medical therapy to the subject, administering an additional surgical therapy to the subject, or administering an alternative surgical therapy to the subject, or a combination thereof. In some embodiments, in the absence of a detected reduction in the amount or activity of FKBP5 protein or expression of the gene encoding FKBP5 protein after administration of the medical or surgical therapy for treatment of hypercortisolemia and relative to a pre-administration or control value, wherein the detected reduction is greater than a threshold value, the method comprises administering an increased amount of a medical therapy to the subject, administering an alternative medical therapy to the subject, administering an additional surgical therapy to the subject, or administering an alternative surgical therapy to the subject, or a combination thereof.

iii. Threshold, Control, and Threshold Difference Values

[0094] FKBP5 amount, expression, or activity can be compared to various threshold, control, or threshold difference values to assess clinical or biochemical response as described herein. Similarly, a change in FKBP5 amount, expression, or activity from pre-administration (*e.g.*, pre-GRA administration or pre-medical or surgical therapy for treatment of hypercortisolemia administration) to post-administration can be compared to various threshold, control, or threshold difference values to assess a clinical or biochemical response

to the administered GRA or other therapy as described herein. In some cases, the threshold, control, or threshold difference value is selected to provide a sufficient sensitivity or specificity for use as a diagnostic. For example, the threshold, control, or threshold difference value can be selected to provide at least a 90% sensitivity, at least a 95% specificity, or the combination thereof. In some cases, the threshold, control, or threshold difference value is derived from a cohort of test individuals, wherein the cohort is of sufficient size to provide the sufficient sensitivity or specificity for use as a diagnostic.

[0095] In some cases, the cohort size is at least 100 or at least 200 test individuals. For example, 100 or 200 healthy (*e.g.*, non-Cushing's, non-hypercortisolemic, or not otherwise in need of a GRA) test individuals can be selected to provide a threshold or control amount, activity, or expression level of FKBP5. As described herein, a measured FKBP5 amount, activity, or expression level in a human subject that is high as compared to a threshold or control level derived from a cohort of at least 100 or at least 200 healthy test individuals can indicate the subject has Cushing's syndrome. Alternatively, as described herein, a cohort of such healthy individuals would be expected to exhibit a small difference in FKBP5 amount, expression, or activity in response to administration of a medical or surgical therapy such as a GRA. As such, a measured reduction in FKBP5 amount, activity, or expression level from pre-administration to post-administration that is greater than (*e.g.*, at least 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, or 50-fold greater than) a threshold difference (*e.g.*, threshold reduction) value derived from a cohort of at least 100 or at least 200 healthy test individuals in response to therapy administration can indicate a clinical or biochemical response to the GRA.

[0096] In some cases, the cohort size is at least 20 or 30 or 50 test individuals. For example, the cohort can comprise or consist of subjects known or suspected of having Cushing's syndrome. In some cases, the cohort of test individuals known or suspected of having Cushing's syndrome is an untreated control cohort. In some cases, the cohort can comprise or consist of subjects having Cushing's syndrome and exhibiting a clinical or biochemical response to an administered GRA or other medical or surgical therapy for treatment of Cushing's, *e.g.*, as indicated by a reduction in, or elimination of, one or more symptoms of Cushing's. As described herein, a measured FKBP5 amount, activity, or expression level that is similar to (*e.g.*, less than 5%, 10%, 25%, 30%, 50%, 75%, or 100% above, or at least 95%, 90%, 80%, 70%, 60%, or 50% of) a threshold value derived from a cohort of 20 or 30 or 50 test individuals known or suspected of having (*e.g.*, untreated)

Cushing's syndrome can indicate that the subject has Cushing's syndrome. In contrast, a measured FKBP5 amount, activity, or expression level that is lower than (*e.g.*, less than 1%, 5%, 10%, 15%, 20%, 25%, or 50% of) a threshold value derived from a cohort of 20 or 30 or 50 test individuals known or suspected of having (*e.g.*, untreated) Cushing's syndrome can indicate that the subject does not have Cushing's syndrome.

[0097] Alternatively, a measured reduction in FKBP5 amount, activity, or expression level from pre-GRA administration to post-GRA administration that is similar to a threshold difference value derived from a cohort of 20 to 30, 20 to 50, 30 to 50, or at least 20, 30, or 50 individuals known or suspected of having Cushing's syndrome and exhibiting a clinical or biochemical response to GRA administration can indicate a clinical or biochemical response to the GRA. In contrast, if the reduction from pre-GRA administration to post-GRA administration does not meet the threshold difference value derived from the cohort of 20 to 30, 20 to 50, 30 to 50, or at least 20, 30, or 50 individuals known or suspected of having Cushing's syndrome and exhibiting a clinical or biochemical response to GRA administration, a lack of a clinical or biochemical response to the GRA is indicated.

[0098] The threshold, control, or threshold difference value derived from the cohort (*e.g.*, a cohort of at least 100 or at least 200 healthy individuals or a cohort of at least 20 to 30, 20 to 50, 30 to 50, or at least 20, 30, or 50 individuals known or suspected of having Cushing's syndrome) can be a contained in a database. In such cases, comparisons to the threshold, control, or threshold difference value can comprise querying the database. In some cases, the comparison further comprises applying a test of statistical significance. In some cases, the test of statistical significance includes a comparison of the relative variability of the amount, activity, or expression level in the cohort to the amount, activity, or expression level in the human subject. In some cases, the test of statistical significance includes a comparison of the relative variability in a change in FKBP5 amount, activity, or expression from pre- to post-medical or surgical therapy administration or from pre- or post-GRA administration in the cohort to the change in the amount, activity, or expression level of FKBP5 in the human subject. In some cases, the methods include identifying whether the comparison is statistically significant in view of the inherent variability of the measurement as indicated by the observed variability in the cohort.

iv. GRA administration

[0099] A GRA administered to the human subject can be any glucocorticoid receptor antagonist, including any of the GRAs described herein. Exemplary GRAs include, but are not limited to, mifepristone, or a heteroaryl-ketone GRA. In some cases, the GRA administered to the human subject is not mifepristone. In some cases, the GRA is a specific GRA that preferentially binds to, and antagonizes, the GR rather than other nuclear receptors, such as mineralocorticoid receptor (MR), androgen receptor (AR), or progesterone receptor (PR). In some cases, the GRA is a pan-specific GRA that preferentially binds to, and antagonizes, the GR and one or two other nuclear receptors selected from the group consisting of MR, AR, and PR. In some cases, the GRA is a non-specific GRA that binds to and antagonizes GR, MR, AR, and PR.

[0100] The GRA can be a steroidal GRA, such as a compound containing a modified cortisol steroid backbone. The two most commonly known classes of structural modifications of the cortisol steroid backbone to create glucocorticoid antagonists include modifications of the 11- β hydroxy group and modification of the 17- β side chain (See, e. g., Lefebvre (1989) J. Steroid Biochem. 33: 557-563). Steroidal GRAs can also include androgen-type steroid compounds as described in U.S. Pat. No. 5,929,058, and the compounds disclosed in U.S. Pat. Nos. 4,296,206; 4,386,085; 4,447,424; 4,477,445; 4,519,946; 4,540,686; 4,547,493; 4,634,695; 4,634,696; 4,753,932; 4,774,236; 4,808,710; 4,814,327; 4,829,060; 4,861,763; 4,912,097; 4,921,638; 4,943,566; 4,954,490; 4,978,657; 5,006,518; 5,043,332; 5,064,822; 5,073,548; 5,089,488; 5,089,635; 5,093,507; 5,095,010; 5,095,129; 5,132,299; 5,166,146; 5,166,199; 5,173,405; 5,276,023; 5,380,839; 5,348,729; 5,426,102; 5,439,913; 5,616,458, 5,696,127, and 6,303,591. Such steroidal GRAs include cortexolone, dexamethasone-oxetanone, 19-nordeoxycorticosterone, 19-norprogesterone, cortisol-21-mesylate; dexamethasone-21-mesylate, 11β-(4-dimethylaminoethoxyphenyl)-17α-propynyl-17β-hydroxy-4,9-estradien-3-one (RU009), and 17β-hydroxy-17α-19-(4-methylphenyl)androsta-4,9(11)-dien-3-one (RU044).

[0101] Other examples of steroidal GRAs are disclosed in Van Kampen *et al.* (2002) Eur. J. Pharmacol. 457(2-3):207, WO 03/043640, EP 0 683 172 B1, and EP 0 763 541 B1, each of which is incorporated herein by reference. EP 0 763 541 B1 and Hoyberg *et al.*, Int'l J. of Neuro-psychopharmacology, 5:Supp. 1, S148 (2002); disclose the compound (11β,17β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one (ORG 34517).

[0102] The GRA can be a non-steroidal GRA. Non-steroidal GRAs do not share structural homology to, or are not modifications of, cortisol. Such compounds include synthetic mimetics and analogs of proteins, including partially peptidic, pseudopeptidic and non-peptidic molecular entities. Non-steroidal GRA compounds also include glucocorticoid receptor antagonists having a cyclohexyl-pyrimidine backbone, a fused azadecalin backbone, a heteroaryl ketone fused azadecalin backbone, or an octahydro fused azadecalin backbone. Exemplary glucocorticoid receptor antagonists having a cyclohexyl-pyrimidine backbone include those described in U.S. Patent No. 8,685,973. Exemplary glucocorticoid receptor antagonists having a fused azadecalin backbone include those described in U.S. Patent Nos. 7,928,237; and 8,461,172. Exemplary glucocorticoid receptor antagonists having a heteroaryl ketone fused azadecalin backbone include those described in U.S. 2014/0038926. Exemplary glucocorticoid receptor antagonists having an octohydro fused azadecalin backbone include those described in U.S. Provisional Patent Appl. No. 61/908,333, entitled Octahydro Fused Azadecalin Glucocorticoid Receptor Modulators, Attorney Docket No. 85178-887884 (007800US), filed on November 25, 2013.

[0103] Examples of non-steroidal GRAs include the GR antagonist compounds disclosed in U.S. Pat. Nos. 5,696,127; 6,051,573; and 6,570,020; the GR antagonist compounds disclosed in US Patent Application 20020077356, the glucocorticoid receptor antagonists disclosed in Bradley *et al.*, J. Med. Chem. 45, 2417-2424 (2002), *e.g.*, 4α(S)-benzyl-2(R)-chloroethynyl-1,2,3,4,4α,9,10,10α(R)-octahydro-phenanthrene-2,7-diol ("CP 394531") and 4α(S)-benzyl-2(R)-prop-1-ynyl-1,2,3,4,4α,9,10,10α(R)-octahydro-phenanthrene-2,7-diol ("CP 409069"); and the compounds disclosed in PCT International Application No. WO 96/19458, which describes non-steroidal compounds which are high-affinity, highly selective antagonists for steroid receptors, such as 6-substituted-1,2-dihydro-N-protected-quinolines.

[0104] The GRAs can be delivered by any suitable means, including oral, parenteral and topical methods. Transdermal administration methods, by a topical route, can be formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0105] The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of a GRA. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the

unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0106] The GRA can be co-administered with other agents. Co-administration includes administering the GRA within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of the other agent. Co-administration also includes administering simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. Moreover, the GRA can each be administered once a day, or two, three, or more times per day so as to provide the preferred dosage level per day.

[0107] In some embodiments, co-administration can be accomplished by co-formulation, *i.e.*, preparing a single pharmaceutical composition including a GRA and any other agent. Alternatively, the various components can be formulated separately. Exemplary compounds, compositions, or active agents that can be co-administered with a GRA include, but are not limited to, another GRA, an agent that inhibits cellular proliferation, an anti-cancer chemotherapeutic, or an antibody.

[0108] The GRA, and any other agents, can be present in any suitable amount, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. Suitable dosage ranges include from about 0.1 mg to about 10,000 mg, or about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg. Suitable dosages also include about 1 mg, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 mg. If the GRA is mifepristone, treatment can be further understood by reference to U.S. Application No. 13/677,465, the disclosure of which is incorporated by reference in its entirety.

[0109] The composition can also contain other compatible therapeutic agents. The therapeutic agents can be used in combination with one another, with other active agents known to be useful in antagonizing a glucocorticoid receptor, or with adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent.

b. Diagnosis of Cushing's syndrome

[0110] Cushing's syndrome can be diagnosed by detecting an amount or activity of FKBP5 protein or an expression level of a gene encoding FKBP5 and correlating the amount, activity, or expression level with a presence or absence, or likelihood, of Cushing's syndrome. The method can include: a) measuring an amount, or activity of FKBP5 protein or

an expression level of a gene encoding FKBP5 in a sample from the subject; and b) identifying the subject as likely to be suffering from Cushing's syndrome when the amount, activity, or expression level is indicative of Cushing's syndrome.

[0111] The sample can be obtained by a variety of means. For example, the sample can be obtained by collecting a blood sample (*e.g.*, a sample of whole blood or a fraction thereof). Alternatively, the sample can be obtained by scraping epithelial cells (*e.g.*, nasal epithelial cells) of a subject. Samples include, but are not limited to samples of human cells and tissues, such as blood samples, cerebrospinal fluid samples, synovial tissue samples, synovial fluid samples, brain tissue samples, blood vessel samples, or tumor (*e.g.*, pituitary adenoma) samples.

[0112] The sample can be extracted to obtain FKBP1 protein, or FKBP5 nucleic acid. For example, cells can be lysed, and the protein fraction obtained. In some cases, the lysate is further fractionated to purify a specified cellular compartment. For example, the cell lysate can be fractionated to obtain a cytosolic protein fraction. As another example, the cell lysate can be fractionated to obtain a nuclear or nucleolar protein fraction. The protein fraction can be assayed for FKBP5 protein levels or activity. Alternatively, the cells can be lysed, and a nucleic acid (*e.g.*, mRNA) fraction obtained. The nucleic acid fraction can be assayed for expression of the FKBP5 gene.

[0113] The cell lysate, or protein fraction thereof can be purified using a variety of methods to obtain a fraction enriched for FKBP5 protein, or a portion thereof. For example, cells can be lysed and contacted with a chromatography medium under conditions suitable to preferentially bind contaminants or target protein. Where contaminants are preferentially bound, target protein can be collected as a flow through fraction and assayed further. Where target protein is bound, the chromatography medium can be washed and the target protein eluted.

[0114] As another example, cells can be lysed and contacted with a capture reagent (*e.g.*, a capture antibody or aptamer) that specifically binds to the FKBP5 protein, or a portion thereof. The capture reagent can be immobilized on a solid support. In some cases, the FKBP5 protein or portion thereof can be eluted from the capture reagent and then detected or quantified. In other cases, the FKBP5 protein or portion thereof can be detected or quantified as a capture reagent-bound form.

[0115] Similarly, the cell lysate, or nucleic acid fraction thereof can be purified using a variety of methods to obtain an fraction enriched for a transcript of a gene encoding FKBP5. For example, cells can be lysed and nucleic acids can be precipitated or otherwise purified from the lysate. In some cases, the nucleic acids can be purified by contacting the sample, or a fraction thereof, with a surface immobilized oligodT moiety to preferentially bind polyadenylated mRNA.

[0116] Nucleic acids can be subject to amplification, hybridization, polymerization, reverse transcription, or a combination thereof. In some cases, the amplification, hybridization, polymerization, or reverse transcription is target specific such that the gene encoding FKBP5, a transcript thereof, or a portion thereof is specifically amplified, hybridized, or reverse transcribed. In some cases, the amplification, hybridization, polymerization, or reverse transcription is not target specific such that the sample is subject to whole genome or whole transcriptome hybridization, polymerization, or reverse transcription. Whole genome or other non-specific hybridization, polymerization, or reverse transcription can be performed with the use of one or more degenerate primers or probes. After non-specific hybridization, polymerization, or reverse transcription, the FKBP5 gene expression can be specifically detected and/or quantified.

[0117] The amount or activity of FKBP5 polypeptide, or a portion thereof, can be measured by a variety of methods known in the art. For example, an ELISA (*e.g.*, sandwich ELISA) can be used to measure polypeptide levels in a sample, or a protein extract thereof, using one or more antibodies specific for the FKBP5 protein, or a portion thereof. In some cases, the ELISA is a sandwich ELISA, in which FKBP5 polypeptide, or a portion thereof, is immobilized by binding to an immobilized capture reagent (*e.g.*, capture antibody or aptamer), and the immobilized polypeptide or portion thereof is detected with a detection reagent (*e.g.*, detection antibody or aptamer).

[0118] As another example, activity of the FKBP5 polypeptide, or a portion thereof, can be measured by contacting the sample, or a protein extract thereof, with a proline containing peptide substrate to measure the FKBP5-mediated cis-trans prolyl isomerase activity of the sample. In some cases, the isomerization of the substrate can be measured using an cis-trans proline isomer sensitive enzyme, such as a protease. For example chymotrypsin, which has a high substrate specificity and catalytic efficiency (k_{cat}/Km) against peptide substrates having a trans-proline at the P2 position and phenylalanine or tyrosine at the P1 position, but very

little or no specificity or catalytic efficiency against such peptides containing a cis-proline at P2, can be used to measure prolyl isomerase activity. For instance, an N-succinyl-Ala-Leu-*cis*-Pro-Phe-*p*-nitroanilide substrate can be used in combination with chymotrypsin, which preferably cleaves the trans prolyl isomer of the substrate to assay a sample or extract thereof for FKBP5 prolyl isomerase activity. The production of the trans isomer of the substrate by isomerase activity of the FKBP5 or portion thereof can be measured by detecting the digestion of the nitroanilide substrate by the chymotrypsin as described, *e.g.*, in Fischer *et al.* Nature. 1989 Feb 2;337(6206):476-8.

[0119] As another example, activity of the FKBP5 polypeptide, or a portion thereof, can be detected or quantified by measuring the amount of FKBP5 protein bound to GR in the sample. This can be performed, *e.g.*, by purifying GR or FKBP5 protein under conditions suitable to preserve binding between GR and FKBP5 protein. The purification product can then be assayed for the presence, absence, or quantity of the cognate binding partner. For example, cytosolic GR can be purified and the presence of FKBP5 protein detected in the purification product. As another example, FKBP5 protein can be purified and the presence of GR can be detected in the purification product. In some cases, this can be performed using a sandwich ELISA-type assay in which the immobilized capture reagent recognizes one member of the GR:FKBP5 protein complex and the detection reagent recognizes the other member of the GR:FKBP5 protein complex.

[0120] As another example, expression of a gene encoding FKBP5 protein can be measured by reverse transcription of FKBP5 mRNA, or a portion thereof, and quantitative amplification of the reverse transcription product or a portion thereof. The quantitative amplification can be performed using PCR (*e.g.*, real time PCR) or other amplification techniques known in the art. The amplification can be detected by, *e.g.*, detecting incorporation of an intercalating dye into the amplification product, degradation of a quenched fluorescence hydrolysis probe, or binding of quenched molecular beacon.

[0121] Any measured amount activity or expression level in a sample can be normalized to a reference. For example, expression level can be normalized to total mRNA levels, or the expression level of a reference gene. Suitable reference genes include, but are not limited to, GAPDH, , hypoxanthine phosphoribosyltransferase 1 (HRPT1), ribosomal protein large P1, or another housekeeping gene. As another example, FKBP5 protein amount can be normalized to total protein levels, or the level of a reference gene product. Suitable reference

gene products include, but are not limited to, actin, tubulin, COX IV, HRPT1, GAPDH, or another housekeeping gene product.

[0122] The amount or activity of FKBP5 protein or expression level of the gene encoding FKBP5 can be compared to a control value or threshold to indicate the presence or absence, or likelihood, of Cushing's syndrome. In some cases, the control or threshold is a positive control, such that when the amount or activity of FKBP5 protein or expression level of the gene encoding FKBP5 is near, equal to, or higher than the control or threshold value, Cushing's syndrome is indicated. In some cases, the control or threshold is a negative control, such that when the amount or activity of FKBP5 protein or expression level of the gene encoding FKBP5 is near, equal to, or below the threshold value, the absence of Cushing's syndrome is indicated.

EXAMPLES

I. Example I

[0123] Ten healthy subjects are treated with prednisone on day -19. On day -12, subjects are treated with prednisone (25 mg) and mifepristone (600 mg). On day 1, subjects are treated with prednisone (25 mg) and CORT125134 (500 mg). Blood samples are taken before each dose and at various time-points after each dose. The study scheme is depicted in FIG. 1. The expression level of the FKBP5 gene is measured in the pre-administration samples obtained before dosing on each day and in the post-administration samples obtained at various time points after dosing on each day. Raw expression level data in the samples are normalized against the expression level of the glyceraldehyde phosphate dehydrogenase (GAPDH) gene in each sample. As illustrated in FIG. 2, the normalized expression level of the FKBP5 gene in the whole blood samples after administration of the GR agonist prednisone is from about 10 to 50 fold above the pre-administration level. Administration of the GRAs mifepristone or CORT125134 causes a significant decrease in the fold change in FKBP5 expression.

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[0124] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference. Where a conflict exists between the instant application and a reference provided herein, the instant application shall dominate.

WHAT IS CLAIMED IS:

1. A method for assessing a biochemical response to a glucocorticoid receptor antagonist (GRA) in a human subject, the method comprising:

a) measuring a first amount, or activity of 51 kDa FK506 binding protein (FKBP5 protein) or a first expression level of a gene encoding FKBP5 protein in a first sample from the subject, wherein:

i) the first sample comprises primary cells; and

ii) the first sample is obtained before the GRA is administered to the subject;

b) measuring a second amount or activity of FKBP5 protein or a second expression level of a gene encoding FKBP5 protein in a second sample from the subject, wherein:

i) the second sample comprises primary cells; and

ii) the second sample is obtained after the GRA is administered to the subject; and

d) comparing the first and second amounts, activities, or expression levels, wherein a reduction in the amount or activity of FKBP5 protein or a reduction in the expression level of the gene encoding FKBP5 protein in the second sample indicates the biochemical response to the GRA.

2. The method of claim 1, wherein the first sample is obtained prior to administering multiple doses of GRA to the subject, and the second sample is obtained after administering the multiple doses of GRA to the subject.

3. The method of claim 1, wherein the measuring of a) and/or b) comprises quantitating an amount of mRNA encoding FKBP5 protein in the sample.

4. The method of claim 1, wherein the measuring of a) and/or b) comprises quantitating the amount of FKBP5 protein in the sample.

5. The method of claim 1, wherein the measuring comprises quantitating the amount of FKBP5 protein activity in the sample.

6. The method of claim 5, wherein the quantitating the amount of FKBP5 protein activity in the sample comprises measuring FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the sample.

7. The method of claim 5, wherein the quantitating the amount of FKBP5 protein activity in the sample comprises measuring the amount of FKBP5 protein bound to glucocorticoid receptor (GR) in the sample.

8. The method of claim 1, wherein the GRA administered to the subject comprises mifepristone.

9. The method of claim 1, wherein the GRA administered to the subject is not mifepristone.

10. The method of claim 9, wherein the GRA administered to the subject comprises a heteroaryl-ketone GRA.

11. The method of claim 1, wherein the first or second samples comprise whole blood, or a fraction thereof.

12. The method of claim 1, wherein the first or second samples comprise nasal epithelial scraping samples.

13. The method of claim 1, wherein the patient is in need of administration of the glucocorticoid receptor antagonist (GRA).

14. The method of claim 13, wherein the patient has elevated levels of cortisol.

15. The method of claim 1, wherein the patient has cancer and the first and second samples comprise tumor cells.

16. The method of claim 1, wherein the first and second samples comprise whole blood, or a fraction thereof.

17. The method of claim 1, wherein the method comprises administering an increased amount of GRA to the subject in the absence of a detected reduction in the

amount or activity of FKBP5 protein or a detected reduction in the expression level of the gene encoding FKBP5 protein in the second sample.

18. A method for diagnosing Cushing's syndrome in a human subject, the method comprising:

a) measuring an amount, or activity of 51 kDa FK506 binding protein (FKBP5 protein) or an expression level of a gene encoding FKBP5 protein in a sample obtained from the subject, wherein the sample comprises primary cells; and

b) identifying the subject as likely to be suffering from Cushing's syndrome when the amount, activity or expression level is high relative to a control.

19. The method of claim 18, wherein the measuring comprises quantitating an amount of mRNA encoding FKBP5 protein in the primary cells of the sample.

20. The method of claim 18, wherein the measuring comprises quantitating the amount of FKBP5 protein in the primary cells of the sample.

21. The method of claim 18, wherein the measuring comprises quantitating the FKBP5 protein activity in the primary cells of the sample.

22. The method of claim 21, wherein the quantitating the FKBP5 protein activity in the primary cells of the sample comprises quantitating FKBP5 protein peptidyl-prolyl-cis-trans isomerase activity in the primary cells of the sample.

23. The method of claim 21, wherein the quantitating the FKBP5 protein activity in the primary cells of the sample comprises quantitating the amount of FKBP5 protein bound to GR in the primary cells of the sample.

24. The method of claim 18, wherein the sample obtained from the subject comprises whole blood, or a fraction thereof.

25. The method of claim 18, wherein the subject has undergone transsphenoidal surgery before the sample is obtained from the subject.

26. The method of claim 18, wherein the method comprises administering a treatment for Cushing's syndrome when the amount or activity of FKBP5 protein or the expression level of the gene encoding FKBP5 protein is high relative to a control.

27. The method of claim 26, wherein the administering the treatment for Cushing's syndrome comprises administering to the subject a glucocorticoid receptor antagonist (GRA).

28. A method for assessing a biochemical response in a human subject to administering to the subject a medical or surgical therapy for treatment of hypercortisolemia, the method comprising:

a) measuring a first amount, or activity of 51 kDa FK506 binding protein (FKBP5 protein) or a first expression level of a gene encoding FKBP5 protein in a first sample from the subject, wherein:

i) the first sample comprises primary cells; and

ii) the first sample is obtained before administering the medical or surgical therapy for treatment of hypercortisolemia to the subject;

b) measuring a second amount or activity of FKBP5 protein or a second expression level of a gene encoding FKBP5 protein in a second sample from the subject, wherein:

i) the second sample comprises primary cells; and

ii) the second sample is obtained after the medical or surgical therapy for treatment of hypercortisolemia is administered to the subject; and

d) comparing the first and second amounts, activities, or expression levels,

wherein a reduction in the amount or activity of FKBP5 protein or a reduction in the expression level of the gene encoding FKBP5 protein in the second sample indicates the biochemical response to the medical or surgical therapy for treatment of hypercortisolemia.

29. The method of claim 28, wherein the medical or surgical therapy for treatment of hypercortisolemia is selected from the group consisting of: inhibition of steroidogenesis, administration of an ACTH modulator, GRA administration, transsphenoidal surgery, repeat transsphenoidal surgery, unilateral adrenalectomy, bilateral adrenalectomy, radiotherapy, resection of a non-pituitary ACTH-secreting tumor, treatment with a peptide receptor radionuclide therapy, and combinations thereof.

30. The method of claim 29, wherein the inhibition of steroidogenesis comprises administration of ketoconazole, levoketoconazole, metyrapone, LCI699, mitotane, aminoglutethimide, etomidate, or a combination thereof.

31. The method of claim 29, wherein the administration of an ACTH modulator comprises administration of a dopamine agonist, somatostatin, a somatostatin analog, retinoic acid, R-roscovitine, or a combination thereof.

32. The method of claim 31, wherein the dopamine agonist is selected from the group consisting of bromocriptine and cabergoline.

33. The method of claim 28, wherein the method comprises administering an additional medical or surgical therapy for treatment of hypercortisolemia in an absence of a detected reduction in the amount or activity of FKBP5 protein or reduction in the expression level of the gene encoding FKBP5 protein in the second sample.

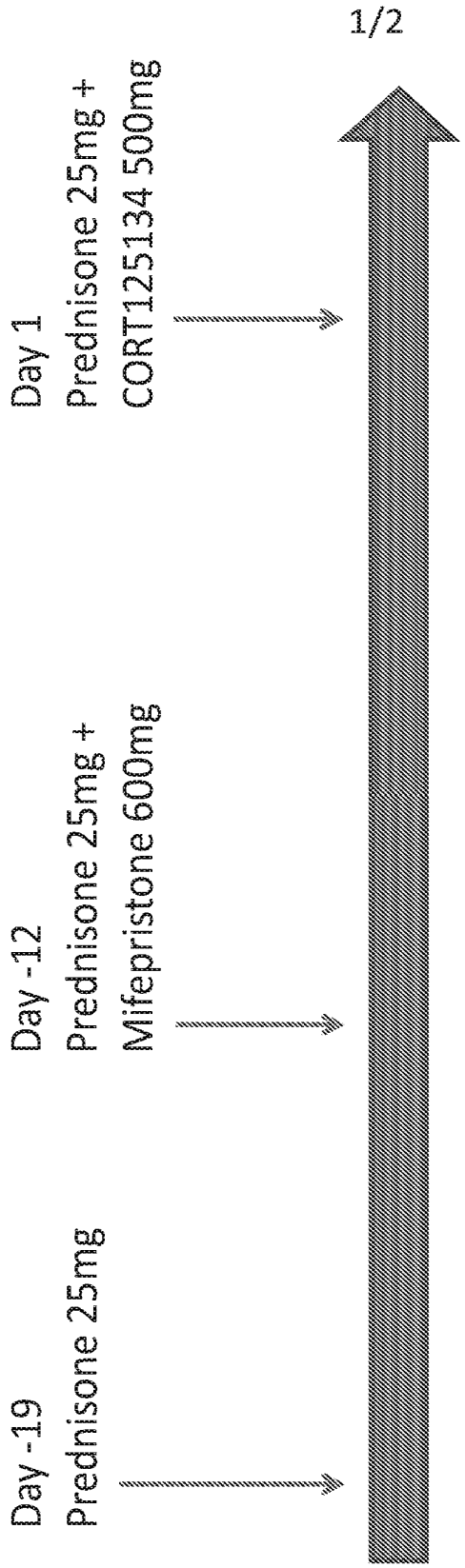
1/2
Day -19
Prednisone 25mg
Day -12
Prednisone 25mg +
Mifepristone 600mg
Day 1
Prednisone 25mg +
CORT125134 500mg

FIG. 1

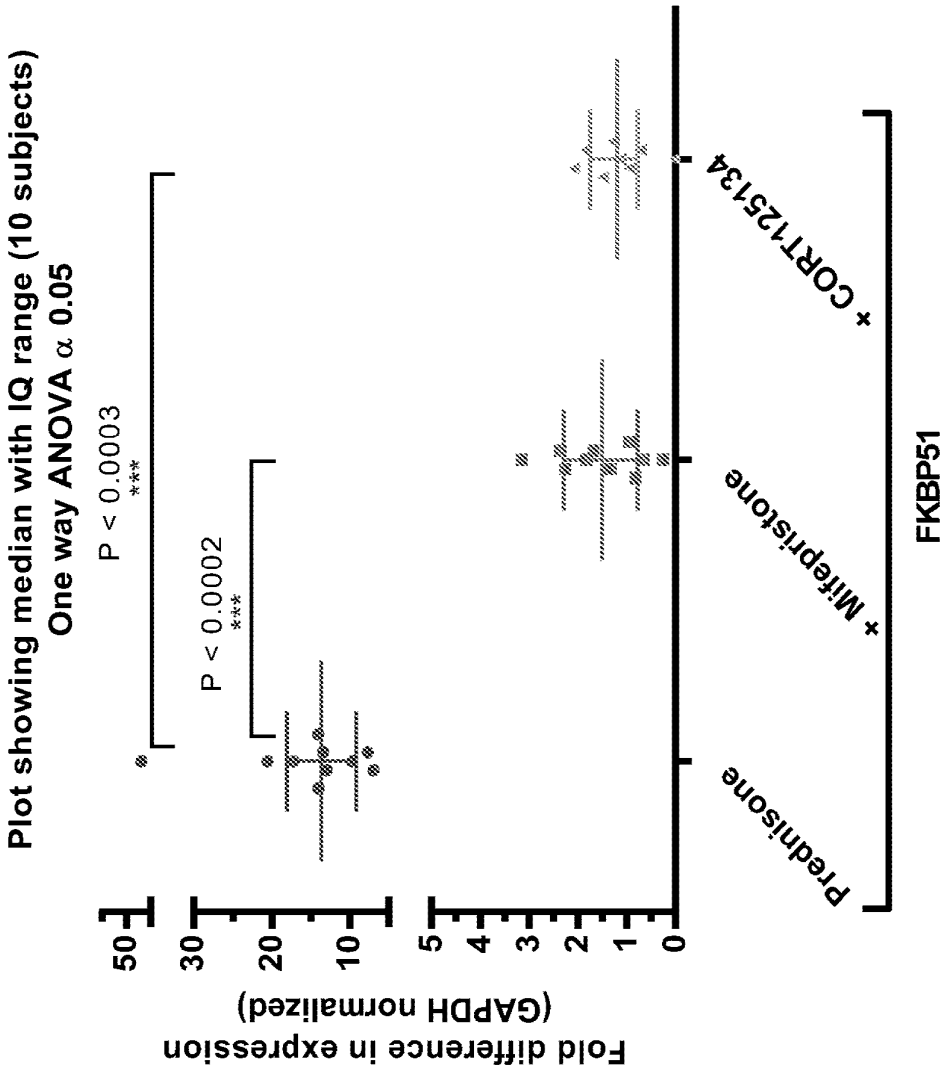
Plot showing median with IQ range (10 subjects)
One way ANOVA α 0.05
P < 0.0003
***
P < 0.0002
***
Fold difference in expression
(GAPDH normalized)
50
30
20
10
5
4
3
2
1
0
Prednisone
+ Mifepristone
+ CORT125134
FKBP51

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/33143

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61P 5/00, A61P 5/46, A61K 45/06 (2016.01)
CPC - A61K 45/00, A61K 45/06, G01N 2333/705
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61P 5/00, A61P 5/46, A61K 45/06 (2016.01)
CPC: A61K 45/00, A61K 45/06, G01N 2333/705

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC: G01N2333/723, G01N2800/52

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, PubWest, Google Scholar, Google Patents: 51 kDa FK506, Cushing's syndrome, glucocorticoid receptor antagonist, GRA, FKBP5, peptidyl- 3 proly1-cis-trans isomerase activity, hypercortisolemia, ketoconazole, levoketoconazole

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	LEE et al., A measure of glucocorticoid load provided by DNA methylation of Fkbp5 in mice. Psychopharmacology (2011) vol 218 pp 303-312; pg 304, col 1, para 1-3, col 2, para 1-2, pg 305, col 2, para 4, Figs. 1B, 2C	18-19, 24, 26 --- 20-23, 25, 27
Y	US 2012/0039812 A1 (HOLSBOER et al.) 16 February 2012 (16.02.2012); para [0015],[0019], [0023], [0025], [0037], [0038],	1-17, 20-23
Y	US 2012/0094945 A1 (DIAMOND et al.) 19 April 2012 (19.04.2012); para [0045], [0065], [0085], [0089], Fig. 4B, Table 2	1-17
Y	US 2014/0170768 A1 (EHRENKRANZ) 19 June 2014 (19.06.2014); Abstract, Table 1, para [0017], [0019], [0021], [0040]	8, 14, 25, 27
Y	WO 2013/177559 A2 (CORCEPT THERAPEUTICS, INC) 28 November 2013 (28.11.2013); abstract; para [0007], [0036], [0046], [0130]	10, 15
Y	GLAXOSMITHKLINE, A Randomised, Double Blind, Placebo Controlled, 4 Period, Incomplete Block, Crossover Study Assessing the Doseresponse Curve of Fluticasone Propionate in an Antigen Challenge Chamber, Clinical Trials, August 23, 2012, [online], [retrieved on 2016-07-13]. Retrieved from <https://clinicaltrials.gov/ct2/show/NCT00848965>; page 2, para 8	12
Y	US 2008/0118521 A1 (SPRING et al.) 22 May 2008 (22.05.2008); para [0092]	6, 22

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 September 2016 (17.09.2016)	05 OCT 2016
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/33143

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-17, directed to a method for assessing a response to a glucocorticoid receptor antagonist in a human subject.

Group II: Claims 18-27 , directed to a method for diagnosing Cushing' s syndrome in a human subject

Group III: Claims 28-33, directed to method for assessing a response to a therapy for treatment of hypercortisolemia in a human subject

*****Continued in Supplemental Box*****

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-27

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

Continuation of Box III: Observations where unity of invention is lacking

The inventions listed as Groups I through III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features

Groups II and III do not require assessing a biochemical response wherein a reduction in FKBP5 amount, activity or expression level indicates that the subject responds to a glucocorticoid receptor antagonist (GRA), as required by group I.

Groups I and III do not require diagnosing Cushing' s syndrome in a human subject based on elevated FKBP5 amount, activity or expression level, as required by group II.

Group I and II do not require assessing a biochemical response wherein a reduction in FKBP5 amount, activity or expression level indicates that the subject responds to a therapy for treatment of hypercortisolemia in a human subject, as required by group III.

Common Technical Features

The common technical feature shared by Groups I through III is measuring an amount, or activity of 51 kDa FK506 binding protein (FKBP5 protein) or an expression level of a gene encoding FKBP5 protein in a sample obtained from the subject. However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is obvious over US 2012/0039812 A1 to HOLSBOER et al. (hereinafter 'Holsboer') (para [0011] "assessing in a sample obtained from said subject the expression level of one or more genes selected from the FK506 binding protein 5 (FKBP5) gene", para [0019] "The human FK506 binding protein 5 (FKBP5) gene located on chromosome 6 (6p21.3-p21.2) encodes the FK505 binding protein 5."). Holsboer does not expressly teach that said subject is human, however, an artisan of ordinary skill would have readily appreciated that measurement of the human FK506 binding protein 5 taught by Holsboer would be performed in a human sample.

A common technical feature shared by Groups I and III is measuring an amount, or activity of 51 kDa FK506 binding protein (FKBP5 protein) or an expression level of a gene encoding FKBP5 protein in first and second subject samples taken before and after a treatment, (e.g., a glucocorticoid receptor (GR) antagonist), wherein a reduction in the amount or activity of FKBP5 protein or a reduction in the expression level of the gene encoding FKBP5 protein in the second sample indicates that the subject respond to the treatment. However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is obvious over Holsboer in view of US 2012/0094945 A1 to DIAMOND et al. (hereinafter, 'Diamond'). Holsboer teaches measuring FKBP5 expression in first and second subject samples, wherein the first sample is or is not first contacted with a test compound capable of preventing or treating PTSD (para [0037] "a method of identifying a compound capable of preventing or treating PTSD ... the method comprising the steps of: (a) assessing the expression level of one or more genes selected from the FK506 binding protein 5 (FKBP5) gene ... in a sample obtained from a subject and contacted with said test compound; and (b) assessing the expression level of said one or more gene(s) in ... a sample obtained from a subject, wherein said cell or sample was i) not contacted with said test compound; ii) contacted with a compound known to not affect the expression levels of said gene(s) of step (a)"). Holsboer does not expressly teach that a reduction in the expression level of the gene encoding FKBP5 protein in the treated sample indicates the biochemical response to the therapy for treatment, however Diamond teaches modulating GR signaling with GR antagonists wherein FKBP5 expression is reduced (para [0065] "a method of modulating a glucocorticoid receptor by administering to a patient in need of such treatment, a therapeutically effective amount of a compound described herein", para [0045] " we identified multiple classes of compounds that modulate GR signaling at endogenous target genes.", para [0089] Ciclopirox olamine, rosolic acid, and pararosaniline, not previously known to modulate GR signaling, were each identified in the primary screen as selective GR antagonists. The steroid hormone hydroxyprogesterone caproate (Hpg), a progestin, also had strong selective effects in the primary screen ... Ciclopirox olamine was a general GR antagonist, whereas Hpg, rosolic acid and pararosaniline selectively modulated endogenous GR target genes similarly to their regulation of the plasmid-based FP reporters (compare FIG. 4B to Table 2). Specifically, Hpg had no impact on induction of ENaC but reduced induction of GILZ and FKBP5, while rosolic acid inhibited GR induction of ENaC and FKBP5, but failed to inhibit GILZ (FIG. 4B).") Based on Diamond's teaching, it would have been obvious to an artisan of ordinary skill to use a reduction of FKBP5 expression in a sample treated with a (for example) GR antagonist compared to the level of FKBP5 expression in an untreated sample as a measure of an effective treatment.

As these technical features were known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Groups I through III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Note: Claims 1 and 27 comprise parts (a), (b) and (d), but do not comprise a part (c). These claims are not changed.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: KENNETH A. WEBER
KILPATRICK TOWNSEND & STOCKTON LLP
MAILSTOP: IP DOCKETING - 22
1100 PEACHTREE STREET, SUITE 2800
ATLANTA, GA 30309

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 15 MAY 2018
Applicant's or agent's file reference 1079597	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 18/20336	International filing date *(day/month/year)* 28 February 2018 (28.02.2018)
Applicant CORCEPT THERAPEUTICS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Lee W. Young PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2014)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 1079597	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 18/20336	International filing date *(day/month/year)* 28 February 2018 (28.02.2018)	(Earliest) Priority Date *(day/month/year)* 01 March 2017 (01.03.2017)
Applicant CORCEPT THERAPEUTICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. 1

☒ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

Form PCT/ISA/210 (first sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/20336

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 8, 16, 23, 27, 31 and 32
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/20336

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/56; A61K 31/497; A61P 43/00 (2018.01)
CPC - A61K 31/567; A61K 31/497; A61K 2300/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MORGAN et al. 'Mifepristone for Management of Cushing's Syndrome', Pharmacotherapy, 2013 Vol.33(3), pp.319-29. doi: 10.1002/phar.1202. Epub 2013 Feb 21. pg 320, col 2, para 3 to pg 321, col 1, para 1; pg 325, col 2, para 2 to pg 326, col 2, para 3; pg 326, col 2, para 5 to pg 327, col 1, para 1	1-7, 9-15, 17-22
Y	WO 2010/052445 A1 (UNIVERSITY OF SHEFFIELD) 14 May 2010 (14.05.2010) pg 3, ln 20-34; pg 6, ln 22-23; pg 7, ln 5-7; pg 9, ln 6-13	1-7, 9-15, 17-22, 24-26, 28-30
Y	FLESERIU et al. 'Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome', J Clin Endocrinol Metab, 2012, Vol.97(6), pp. 2039-2049. abstract; pg 2040, col 2, para 2 to para 5; pg 2043, Fig 2	24-26, 28-30
A	WO 2016/187347 A1 (CORCEPT THERAPEUTICS, INC.) 24 November 2016 (24.11.2016) Entire Document	1-7, 9-15, 17-22, 24-26, 28-30
A	US 2010/0135956 A1 (GANT et al.) 03 June 2010 (03.06.2010) Entire Document	1-7, 9-15, 17-22, 24-26, 28-30
A	VARIS et al. The effect of itraconazole on the pharmacokinetics and pharmacodynamics of oral prednisolone. Eur J Clin Pharmacol. 2000, Vol.56(1), pp 57-60. Entire Document	1-7, 9-15, 17-22, 24-26, 28-30

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 April 2018	15 MAY 2018
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: KENNETH A. WEBER
KILPATRICK TOWNSEND & STOCKTON LLP
MAILSTOP: IP DOCKETING - 22
1100 PEACHTREE STREET, SUITE 2800
ATLANTA, GA 30309

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	15 MAY 2018
Applicant's or agent's file reference 1079597	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 18/20336	28 February 2018 (28.02.2018)	01 March 2017 (01.03.2017)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/56; A61K 31/497; A61P 43/00 (2018.01)
CPC - A61K 31/567; A61K 31/497; A61K 2300/00

Applicant CORCEPT THERAPEUTICS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	12 April 2018	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (January 2015)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/20336

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a)).

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Form PCT/ISA/237 (Box No. I) (January 2015)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/20336

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 8, 16, 23, 27, 31 and 32

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. see below are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 8, 16, 23, 27, 31 and 32 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 8, 16, 23, 27, 31 and 32

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

Form PCT/ISA/237 (Box No. III) (January 2015)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/20336

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-7, 9-15, 17-22, 24-26, 28-30	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-7, 9-15, 17-22, 24-26, 28-30	NO
Industrial applicability (IA)	Claims	1-7, 9-15, 17-22, 24-26, 28-30	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-7, 9-15 and 17-22 lack an inventive step under PCT Article 33(3) as being obvious over the article entitled, 'Mifepristone for Management of Cushing's Syndrome' by Morgan et al. (hereinafter 'Morgan') in view of WO 2010/052445 A1 to University of Sheffield (Hereinafter 'Sheffield').

Regarding claim 1, Morgan teaches a method of treating Cushing's' s syndrome in a patient who is taking a glucocorticoid receptor modulator (GRM) once per day (pg 325, col 2, para 2 to pg 326, col 2, para 3, mifepristone) comprising reducing the once-daily dose of said GRM from an original once-daily (OD) dose (pg 326, col 1, para 1, maximum dosage of 900-1200 mg/day based on weight) to an adjusted OD dose that is at least 25% less than said original OD dose, if the patient receives concomitant administration of a CYP3A inhibitor (pg 326, col 2, para 5 to pg 327, col 1, para 1, dose of mifepristone should not exceed 300 mg/day if used in combination with ketoconazole). Morgan does not specifically teach a method wherein the patient who is taking a glucocorticoid receptor modulator (GRM) once per day is receiving concomitant administration of a CYP3A inhibitor. However, Sheffield teaches a method of administering a combination of a glucocorticoid receptor modulator and ketoconazole [which is a CYP3A inhibitor according to instant claim 26] (pg 7, ln 5-7; pg 6, ln 22-23) for reducing cortisol production in a patient with subclinical Cushing's syndrome (pg 3, ln 20-34; pg 7, ln 5-7). It would have been obvious to one of ordinary skill in the art to combine the teachings of Morgan and Sheffield, as both are directed to treating Cushing's syndrome, and to devise a combination therapy for Cushing's syndrome, wherein a reduced dose of mifepristone as disclosed in Morgan is administered with the CYP3A inhibitor, ketoconazole, in order to effectively reduce cortisol production in the treated patient (Sheffield, pg 9, ln 6-13) and thereby provide therapeutic relief from Cushing's syndrome.

Regarding claim 2, Morgan and Sheffield teach the method of claim 1, as above, wherein Morgan teaches that said original once-daily (OD) dose is 1200 milligrams (mg) per day of said GRM (pg 326, col 1, para 1, maximum dosage of 900-1200 mg/day based on weight), and said adjusted OD dose is 300 mg per day of said GRM (pg 326, col 2, para 5 to pg 327, col 1, para 1). Morgan or Sheffield does not teach an adjusted dose of 900 mg/day. However, based on the combined teachings of Morgan and Sheffield, it would have been obvious to one of ordinary skill in the art to arrive at an adjusted dose of 900 mg/day of the GRM, by taking into consideration the age, weight and medical condition of the patient treated, through routine experimentation, in order to effectively reduce cortisol production in the treated patient (Sheffield, pg 9, ln 6-13) and thereby treat Cushing's syndrome in said patient.

Regarding claim 3, Morgan and Sheffield teach the method of claim 1, as above, wherein Morgan teaches that said original once-daily (OD) dose is selected from greater than 800 milligrams (mg) per day, 900 mg per day, and 1200 milligrams (mg) per day of said GRM (pg 326, col 1, para 1, maximum dosage of 900-1200 mg/day based on weight), and said adjusted OD dose is 300 mg per day of said GRM (pg 326, col 2, para 5 to pg 327, col 1, para 1). Morgan or Sheffield does not teach an adjusted dose selected from greater than 800 mg per day and 600 mg/day. However, based on the combined teachings of Morgan and Sheffield, it would have been obvious to one of ordinary skill in the art to arrive at an adjusted dose of greater than 800 mg per day or 600 mg/day of the GRM, by taking into consideration the age, weight and medical condition of the patient treated, through routine experimentation, in order to effectively reduce cortisol production in the treated patient (Sheffield, pg 9, ln 6-13) and thereby treat Cushing's syndrome in said patient.

Regarding claim 4, Morgan and Sheffield teach the method of claim 1, as above, wherein Morgan teaches that said original once-daily (OD) dose is selected from 1200 milligrams (mg) per day and 900 mg per day of said GRM (pg 326, col 1, para 1, maximum dosage of 900-1200 mg/day based on weight), and said adjusted OD dose is 300 mg per day of said GRM (pg 326, col 2, para 5 to pg 327, col 1, para 1).

Regarding claim 5, Morgan and Sheffield teach the method of claim 1, as above, wherein Morgan teaches that said original once-daily (OD) dose is selected from 1200 milligrams (mg) per day, 900 mg per day and greater than 800 mg per day of said GRM (pg 326, col 1, para 1, maximum dosage of 900-1200 mg/day based on weight), and said adjusted OD dose is 300 mg per day of said GRM (pg 326, col 2, para 5 to pg 327, col 1, para 1). Morgan or Sheffield does not teach the method further comprising titrating the adjusted OD dose to 900 mg per day, greater than 800 mg per day, or 600 mg per day of said GRM. However, based on the combined teachings of Morgan and Sheffield, it would have been obvious to one of ordinary skill in the art to titrate the adjusted OD dose to 900 mg per day, greater than 800 mg per day or 600 mg/day of the GRM, by taking into consideration the age, weight and medical condition of the patient treated, through routine experimentation, in order to effectively reduce cortisol production in the treated patient (Sheffield, pg 9, ln 6-13) and thereby treat Cushing's syndrome in said patient.

---Continued in Supplemental Box----

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/20336

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V.2. Citations and Explanations:

Regarding claim 6, Morgan and Sheffield teach the method of claim 1, as above, wherein Morgan teaches that said original once-daily (OD) dose is 600 milligrams (mg) per day of said GRM (pg 326, col 1, para 1, mifepristone, 600 mg/day), and said adjusted OD dose is 300 mg per day of said GRM (pg 326, col 2, para 5 to pg 327, col 1, para 1). Morgan or Sheffield does not teach the method further comprising titrating the adjusted OD dose to 600 mg per day of said GRM. However, based on the combined teachings of Morgan and Sheffield, it would have been obvious to one of ordinary skill in the art to titrate the adjusted OD dose to 600 mg per day of said GRM, by taking into consideration the age, weight and medical condition of the patient treated, through routine experimentation, in order to effectively reduce cortisol production in the treated patient (Sheffield, pg 9, ln 6-13) and thereby treat Cushing's syndrome in said patient.

Regarding claim 7, Morgan and Sheffield teach the method of any of claims 1 to 6, as above, wherein Morgan teaches that said GRM is mifepristone and said CYP3A inhibitor is a strong CYP3A inhibitor (pg 326, col 2, para 5 to pg 327, col 1, para 1, the combination of mifepristone with ketoconazole).

Regarding claim 9, Morgan teaches a method of treating symptoms associated with elevated cortisol levels in a patient (pg 320, col 2, para 3 to pg 321, col 1, para 1) who is taking a glucocorticoid receptor modulator (GRM) once per day (pg 325, col 2, para 2 to pg 326, col 2, para 3, mifepristone) comprising reducing the once-daily dose of said GRM from an original once-daily (OD) dose (pg 326, col 1, para 1, maximum dosage of 900-1200 mg/day based on weight) to an adjusted OD dose that is at least 25% less than said original OD dose, if the patient receives concomitant administration of a CYP3A inhibitor (pg 326, col 2, para 5 to pg 327, col 1, para 1, dose of mifepristone should not exceed 300 mg/day if used in combination with ketoconazole). Morgan does not specifically teach a method wherein the treated patient who is taking a glucocorticoid receptor modulator (GRM) once per day is receiving concomitant administration of a CYP3A inhibitor. However, Sheffield teaches a method of administering a combination of a glucocorticoid receptor modulator and ketoconazole [which is a CYP3A inhibitor according to instant claim 26] (pg 7, ln 5-7; pg 6, ln 22-23) for reducing cortisol production in a patient with subclinical Cushing's syndrome (pg 3, ln 20-34; pg 7, ln 5-7). It would have been obvious to one of ordinary skill in the art to combine the teachings of Morgan and Sheffield, as both are directed to treating Cushing's syndrome, and to devise a combination therapy, wherein a reduced dose of mifepristone as disclosed in Morgan is administered with the CYP3A inhibitor, ketoconazole, in order to effectively reduce cortisol production in the treated patient (Sheffield, pg 9, ln 6-13) and thereby provide therapeutic relief from Cushing's syndrome.

Regarding claim 10, Morgan and Sheffield teach the method of claim 9, as above, wherein Morgan teaches that said original once-daily (OD) dose is 1200 milligrams (mg) per day of said GRM (pg 326, col 1, para 1, maximum dosage of 900-1200 mg/day based on weight), and said adjusted OD dose is 300 mg per day of said GRM (pg 326, col 2, para 5 to pg 327, col 1, para 1). Morgan or Sheffield does not teach an adjusted dose of 900 mg/day. However, based on the combined teachings of Morgan and Sheffield, it would have been obvious to one of ordinary skill in the art to arrive at an adjusted dose of 900 mg/day of the GRM, by taking into consideration the age, weight and medical condition of the patient treated, through routine experimentation, in order to effectively reduce cortisol production in the treated patient (Sheffield, pg 9, ln 6-13) and thereby treat Cushing's syndrome in said patient.

Regarding claim 11, Morgan and Sheffield teach the method of claim 9, as above, wherein Morgan teaches that said original once-daily (OD) dose is selected from greater than 800 milligrams (mg) per day, 900 mg per day, and 1200 milligrams (mg) per day of said GRM (pg 326, col 1, para 1, maximum dosage of 900-1200 mg/day based on weight), and said adjusted OD dose is 300 mg per day of said GRM (pg 326, col 2, para 5 to pg 327, col 1, para 1). Morgan or Sheffield does not teach an adjusted dose selected from greater than 800 mg per day and 600 mg/day. However, based on the combined teachings of Morgan and Sheffield, it would have been obvious to one of ordinary skill in the art to arrive at an adjusted dose of greater than 800 mg per day or 600 mg/day of the GRM, by taking into consideration the age, weight and medical condition of the patient treated, through routine experimentation, in order to effectively reduce cortisol production in the treated patient (Sheffield, pg 9, ln 6-13) and thereby treat Cushing's syndrome in said patient.

Regarding claim 12, Morgan and Sheffield teach the method of claim 9, as above, wherein Morgan teaches that said original once-daily (OD) dose is selected from 1200 milligrams (mg) per day and 900 mg per day of said GRM (pg 326, col 1, para 1, maximum dosage of 900 -1200 mg/day based on weight), and said adjusted OD dose is 300 mg per day of said GRM (pg 326, col 2, para 5 to pg 327, col 1, para 1).

Regarding claim 13, Morgan and Sheffield teach the method of claim 9, as above, wherein Morgan teaches that said original once-daily (OD) dose is selected from 1200 milligrams (mg) per day, 900 mg per day and greater than 800 mg per day of said GRM (pg 326, col 1, para 1, maximum dosage of 900-1200 mg/day based on weight), and said adjusted OD dose is 300 mg per day of said GRM (pg 326, col 2, para 5 to pg 327, col 1, para 1). Morgan or Sheffield does not teach the method further comprising titrating the adjusted OD dose to 900 mg per day, greater than 800 mg per day, or 600 mg per day of said GRM. However, based on the combined teachings of Morgan and Sheffield, it would have been obvious to one of ordinary skill in the art to titrate the adjusted OD dose to 900 mg per day, greater than 800 mg per day or 600 mg/day of the GRM, by taking into consideration the age, weight and medical condition of the patient treated, through routine experimentation, in order to effectively reduce cortisol production in the treated patient (Sheffield, pg 9, ln 6-13) and thereby treat Cushing's syndrome in said patient.

Regarding claim 14, Morgan and Sheffield teach the method of claim 9, as above, wherein Morgan teaches that said original once-daily (OD) dose is 600 milligrams (mg) per day of said GRM (pg 326, col 1, para 1, mifepristone, 600 mg/day), and said adjusted OD dose is 300 mg per day of said GRM (pg 326, col 2, para 5 to pg 327, col 1, para 1). Morgan or Sheffield does not teach the method further comprising titrating the adjusted OD dose to 600 mg per day of said GRM. However, based on the combined teachings of Morgan and Sheffield, it would have been obvious to one of ordinary skill in the art to titrate the adjusted OD dose to 600 mg per day of said GRM, by taking into consideration the age, weight and medical condition of the patient treated, through routine experimentation, in order to effectively reduce cortisol production in the treated patient (Sheffield, pg 9, ln 6-13) and thereby treat Cushing's syndrome in said patient.

---Continued in Next Supplemental Box---

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/20336

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Previous Supplemental Box:

Regarding claim 15, Morgan and Sheffield teach the method of any of claims 9 to 14, as above, wherein Morgan teaches that said GRM is mifepristone and said CYP3A inhibitor is a strong CYP3A inhibitor (pg 326, col 2, para 5 to pg 327, col 1, para 1, the combination of mifepristone with ketoconazole).

Regarding claim 17, Morgan teaches a method of controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome (pg 320, col 2, para 3 to pg 321, col 1, para 1, The excess cortisol seen in Cushing.s syndrome results in hypertension, hyperglycemia,..) who is taking a glucocorticoid receptor modulator (GRM) once per day (pg 325, col 2, para 2 to pg 326, col 2, para 3, mifepristone) comprising reducing the once-daily dose of said GRM from an original once-daily (OD) dose (pg 326, col 1, para 1, maximum dosage of 900-1200 mg/day based on weight) to an adjusted OD dose that is at least 25% less than said original OD dose, if the patient receives concomitant administration of a CYP3A inhibitor (pg 326, col 2, para 5 to pg 327, col 1, para 1, dose of mifepristone should not exceed 300 mg/day if used in combination with ketoconazole). Morgan does not specifically teach a method wherein the treated patient who is taking a glucocorticoid receptor modulator (GRM) once per day is receiving concomitant administration of a CYP3A inhibitor. However, Sheffield teaches a method of administering a combination of a glucocorticoid receptor modulator and ketoconazole [which is a CYP3A inhibitor according to instant claim 26] (pg 7, ln 5-7; pg 6, ln 22-23) for reducing cortisol production in a patient with subclinical Cushing's syndrome (pg 3, ln 20-34; pg 7, ln 5-7). It would have been obvious to one of ordinary skill in the art to combine the teachings of Morgan and Sheffield, as both are directed to treating Cushing's syndrome, and to devise a combination therapy for controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome, wherein a reduced dose of mifepristone as disclosed in Morgan is administered with the CYP3A inhibitor, ketoconazole, in order to effectively reduce cortisol production in the treated patient (Sheffield, pg 9, ln 6-13) and thereby control hyperglycemia secondary to hypercortisolism in said patient.

Regarding claim 18, Morgan and Sheffield teach the method of claim 17, as above, wherein Morgan teaches that said original once-daily (OD) dose is 1200 milligrams (mg) per day of said GRM (pg 326, col 1, para 1, maximum dosage of 900-1200 mg/day based on weight), and said adjusted OD dose is 300 mg per day of said GRM (pg 326, col 2, para 5 to pg 327, col 1, para 1). Morgan or Sheffield does not teach an adjusted dose of 900 mg/day. However, based on the combined teachings of Morgan and Sheffield, it would have been obvious to one of ordinary skill in the art to arrive at an adjusted dose of 900 mg/day of the GRM, by taking into consideration the age, weight and medical condition of the patient treated, through routine experimentation, in order to effectively reduce cortisol production in the treated patient (Sheffield, pg 9, ln 6-13) and thereby control hyperglycemia secondary to hypercortisolism in said patient.

Regarding claim 19, Morgan and Sheffield teach the method of claim 17, as above, wherein Morgan teaches that said original once-daily (OD) dose is selected from greater than 800 milligrams (mg) per day, 900 mg per day, and 1200 milligrams (mg) per day of said GRM (pg 326, col 1, para 1, maximum dosage of 900-1200 mg/day based on weight), and said adjusted OD dose is 300 mg per day of said GRM (pg 326, col 2, para 5 to pg 327, col 1, para 1). Morgan or Sheffield does not teach an adjusted dose selected from greater than 800 mg per day and 600 mg/day. However, based on the combined teachings of Morgan and Sheffield, it would have been obvious to one of ordinary skill in the art to arrive at an adjusted dose of greater than 800 mg per day or 600 mg/day of the GRM, by taking into consideration the age, weight and medical condition of the patient treated, through routine experimentation, in order to effectively reduce cortisol production in the treated patient (Sheffield, pg 9, ln 6-13) and thereby control hyperglycemia secondary to hypercortisolism in said patient.

Regarding claim 20, Morgan and Sheffield teach the method of claim 17, as above, wherein Morgan teaches that said original once-daily (OD) dose is selected from 1200 milligrams (mg) per day, 900 mg per day and greater than 800 mg per day of said GRM (pg 326, col 1, para 1, maximum dosage of 900-1200 mg/day based on weight), and said adjusted OD dose is 300 mg per day of said GRM (pg 326, col 2, para 5 to pg 327, col 1, para 1). Morgan or Sheffield does not teach the method further comprising titrating the adjusted OD dose to 900 mg per day, greater than 800 mg per day, or 600 mg per day of said GRM. However, based on the combined teachings of Morgan and Sheffield, it would have been obvious to one of ordinary skill in the art to titrate the adjusted OD dose to 900 mg per day, greater than 800 mg per day or 600 mg/day of the GRM, by taking into consideration the age, weight and medical condition of the patient treated, through routine experimentation, in order to effectively reduce cortisol production in the treated patient (Sheffield, pg 9, ln 6-13) and thereby control hyperglycemia secondary to hypercortisolism in said patient.

Regarding claim 21, Morgan and Sheffield teach the method of claim 17, as above, wherein Morgan teaches that said original once-daily (OD) dose is 600 milligrams (mg) per day of said GRM (pg 326, col 1, para 1, mifepristone, 600 mg/day), and said adjusted OD dose is 300 mg per day of said GRM (pg 326, col 2, para 5 to pg 327, col 1, para 1). Morgan or Sheffield does not teach the method further comprising titrating the adjusted OD dose to 600 mg per day of said GRM. However, based on the combined teachings of Morgan and Sheffield, it would have been obvious to one of ordinary skill in the art to titrate the adjusted OD dose to 600 mg per day of said GRM, by taking into consideration the age, weight and medical condition of the patient treated, through routine experimentation, in order to effectively reduce cortisol production in the treated patient (Sheffield, pg 9, ln 6-13) and thereby control hyperglycemia secondary to hypercortisolism in said patient.

Regarding claim 22, Morgan and Sheffield teach the method of any of claims 17 to 21, as above, wherein Morgan teaches that said GRM is mifepristone and said CYP3A inhibitor is a strong CYP3A inhibitor (pg 326, col 2, para 5 to pg 327, col 1, para 1, the combination of mifepristone with ketoconazole).

----Continued in Next Supplemental Box---

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/20336

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Previous Supplemental Box:

Claims 24-26 and 28-30 lack an inventive step under PCT Article 33(3) as being obvious over the article entitled, "Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome', by Fleseriu et al. (hereinafter 'Fleseriu') in view of Sheffield.

Regarding claim 24, Fleseriu teaches a method of controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome (abstract, endogenous CS associated with ..impaired glucose tolerance; pg 2040, col 2, para 2 to para 5; pg 2043, Fig 2) comprising administering a once-daily dose of greater than 800 milligrams (mg) per day, 900 mg per day, and 1200 mg per day, of a glucocorticoid receptor modulator (GRM) (pg 2040, col 2, para 5, mifepristone, 900 mg/day at wk 6 and 1200 mg/d at wk 10).
Fleseriu does not teach said administration when the patient is receiving concomitant administration of a CYP3A inhibitor.
However, Sheffield teaches a method of administering a combination of a glucocorticoid receptor modulator and ketoconazole [which is a CYP3A inhibitor according to instant claim 26] (pg 7, ln 5-7; pg 6, ln 22-23) for reducing cortisol production in a patient with subclinical Cushing's syndrome (pg 3, ln 20-34; pg 7, ln 5-7). It would have been obvious to one of ordinary skill in the art to combine the teachings of Fleseriu and Sheffield, as both are directed to treating Cushing's syndrome, to devise a combination therapy for controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome, wherein mifepristone is administered concomitantly with the CYP3A inhibitor, ketoconazole, and optimize the dose of mifepristone administered to the patient, by taking into consideration the age, weight and medical condition of said patient, through routine experimentation, in order to effectively reduce cortisol production in the treated patient (Sheffield, pg 9, ln 6-13) and thereby control hyperglycemia secondary to hypercortisolism in said patient.

Regarding claim 25, Fleseriu and Sheffield teach the method of claim 24, as above, wherein Fleseriu further teaches that the GRM is mifepristone (abstract; pg 2040, col 2, para 5).

Regarding claim 26, Fleseriu and Sheffield teach the method of claim 24 or 25, as above, wherein Sheffield further teaches that the CYP3A inhibitor is ketoconazole (pg 7, ln 5-7; pg 6, ln 22-23).

Regarding claim 28, Fleseriu teaches the use of a glucocorticoid receptor modulator (GRM) to control hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome (abstract, endogenous CS associated with ..impaired glucose tolerance; pg 2040, col 2, para 2 to para 5; pg 2043, Fig 2). Fleseriu does not teach said use when the patient is receiving concomitant administration of a CYP3A inhibitor. However, Sheffield teaches use of a combination of a glucocorticoid receptor modulator and ketoconazole [which is a CYP3A inhibitor according to instant claim 26] (pg 7, ln 5-7; pg 6, ln 22-23) for reducing cortisol production in a patient with subclinical Cushing's syndrome (pg 3, ln 20-34; pg 7, ln 5-7). It would have been obvious to one of ordinary skill in the art to combine the teachings of Fleseriu and Sheffield, as both are directed to treating Cushing's syndrome, and to use a combination of mifepristone and the CYP3A inhibitor, ketoconazole, in order to effectively reduce cortisol production (Sheffield, pg 9, ln 6-13) and thereby control hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome.

Regarding claim 29, Fleseriu and Sheffield teach the method of claim 28, as above, wherein Fleseriu further teaches that the GRM is mifepristone (abstract; pg 2040, col 2, para 5).

Regarding claim 30, Fleseriu and Sheffield teach the method of claim 28 or 29, as above, wherein Sheffield further teaches that the CYP3A inhibitor is ketoconazole (pg 7, ln 5-7; pg 6, ln 22-23).

Claims 1-7, 9-15, 17-22, 24-26 and 28-30 have industrial applicability as defined by PCT Article 33(4), because the subject matter can be made or used in industry.

Electronic Patent Application Fee Transmittal

Application Number:	15627359
Filing Date:	19-Jun-2017
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Filer:	Kenneth A. Weber/Jo Ann Honcik Dallara
Attorney Docket Number:	085178-1053027-011410US

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	2806	1	120	120
		Total in USD ($)		**120**

Electronic Acknowledgement Receipt

EFS ID:	32761624
Application Number:	15627359
International Application Number:	
Confirmation Number:	2957
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	144579
Filer:	Kenneth A. Weber/Jo Ann Honcik Dallara
Filer Authorized By:	Kenneth A. Weber
Attorney Docket Number:	085178-1053027-011410US
Receipt Date:	30-MAY-2018
Filing Date:	19-JUN-2017
Time Stamp:	17:12:03
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$120
RAM confirmation Number	053118INTEFSW17131500
Deposit Account	201430
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The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	IDS5_Transmittal_1053027.pdf	92742 e1219c4516f98e1cb590dbd31dc4467fac5b11c9	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	IDS5_SB08A_1053027.pdf	123483 eae5691561984e137e6e36e13d8294ce45922721	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	E4_WO_2010052445_A1.pdf	1007328 b4164bec7dbcfe9d0cb8f507181e3ae09e3f2d8e	no	37
Warnings:					
Information:					
4	Foreign Reference	E5_WO_2016187347_A1.pdf	4326744 c4aba4d8348c4c74e2502ce8679f5bbf66e30b79	no	53
Warnings:					
Information:					
5	Non Patent Literature	E6_NPL_Morgan.PDF	908356 d54b6985e1778bfecc03f56520603e4f0f8c1104	no	11
Warnings:					
Information:					
6	Non Patent Literature	E7_NPL_Varis.PDF	347282 cfad0258b46626a930c4a317dd45dbe66b608fe8	no	4
Warnings:					

Information:					
7	Other Reference-Patent/App/Search documents	E8_NPL_PCTUS2018020336_ISR_WO_05152018.pdf	701886 478fb3e2b4c21dc8ae860e6934685b965b769310	no	11
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	30916 cf2b305304b9c2032343014d842985e769142f91	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	7538737	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on May 30, 2018.

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Jo Ann Honcik Dallara/
Jo Ann Honcik Dallara

PATENT
Attorney Docket No.: 085178-1053027-011410US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Confirmation No.: 2957
Joseph K. Belanoff	Examiner: Chris E. Simmons
Application No.: 15/627,359	Technology Center/Art Unit: 1629
Filed: June 19, 2017	
For: CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS	INFORMATION DISCLOSURE STATEMENT
Customer No.: 144579	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

The references cited on attached form PTO/SB/08A are being called to the attention of the Examiner. In accordance with the provisions of 37 CFR §1.98(a)(2), copies of any cited U.S. Patent and U.S. Patent Application Publications are not provided. Copies of the remaining cited references are provided.

It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information. This Information Disclosure Statement is being filed after the mailing of the first Office Action on the merits, but before the mailing date of the final Office Action, Notice of Allowance, or any other action that closes prosecution.

The Commissioner is authorized to charge the fee set forth in §1.17(p) to the firm's credit card for consideration of this paper. The Commissioner is authorized to charge any additional fee due to Deposit Account No. 20-1430.

Respectfully submitted,

/Kenneth A. Weber/

Kenneth A. Weber
Registration No. 31,677

KILPATRICK TOWNSEND & STOCKTON LLP

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/627,359	06/19/2017	Joseph K. Belanoff	085178-1053027-011410US	2957

144579 7590 06/12/2018

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1100 Peachtree Street
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UNITED STATES OF AMERICA

EXAMINER
SIMMONS, CHRIS E

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
06/12/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

KTSDocketing2@kilpatrick.foundationip.com
ipefiling@kilpatricktownsend.com
jfox@corcept.com

Office Action Summary	Application No. 15/627,359	Applicant(s) Belanoff, Joseph K.	
	Examiner CHRIS E SIMMONS	Art Unit 1629	AIA Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 12/15/17 and 1/22/18.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-30 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-30 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 11/1/17 & 12/15/17.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Status

Claims 1-30 are pending. 1-6, 9-24, 27, 28 and 30 stand amended. No claims are canceled or withdrawn. Therefore, Claims 1-30 are examined.

Priority

This application claims the benefit of and priority to U.S. Provisional Application Serial No. 62/465,772, filed March 1, 2017, and U.S. Provisional Application Serial No. 62/466,867, filed March 3, 2017.

Information Disclosure Statement

The Information Disclosure Statement(s) filed 11/1/2017 and 12/15/2017 has/have been considered by the Examiner. The submission(s) is/are in compliance with the provisions of 37 CFR §§ 1.97 and 1.98. Enclosed with this Office Action is a return-copy of the Forms PTO-1449 with the Examiner's signature and indication of those references that have been considered.

Claim Rejections - 35 USC § 103

Maintained - Claim 1-30 is/are rejected under 35 U.S.C. 103 as being unpatentable over Korlym™ (mifepristone) [package insert]. Corcept Therapeutics, Inc., Menlo Park, CA; Feb. 2012. 26 pages in view of Ulmann (US 2010/0261693).

Claimed invention

Claim 1. A method of treating Cushing's syndrome in a patient who is taking a once-daily (OD) dose of a glucocorticoid receptor antagonist (GRA), said OD dose having an original OD dose amount of said GRA, comprising

reducing the amount of the OD dose from said original OD dose amount to an adjusted OD dose amount that is at least 33% less than said original OD dose amount when the patient is receiving concomitant administration of a CYP3A inhibitor,

wherein said original OD dose amount is selected from 900 milligrams (mg) per day and 1200 mg per day of said GRA, and said adjusted OD dose amount is 600 mg per day of said GRA.

Claim 10. A method of treating symptoms associated with elevated cortisol levels in a patient who is taking a once-daily (OD) dose of a glucocorticoid receptor antagonist (GRA), said OD dose having an original OD dose amount of said GRA, comprising reducing the amount of the OD dose from an said original OD dose amount to an adjusted OD dose amount that is at least 33% less than said original OD dose amount when the patient is receiving concomitant administration of a CYP3A inhibitor, wherein said original OD dose amount is selected from 900 milligrams (mg) per day and 1200 mg per day of said GRA, and said adjusted OD dose amount is 600 mg per day of said GRA.

Claim 19. A method of controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome who is taking a once-daily (OD) dose of a glucocorticoid receptor antagonist (GRA), said OD dose having an original OD dose amount of

said GRA, comprising reducing the amount of the OD dose from said original OD dose amount to an adjusted OD dose amount that is at least 33% less than said original OD dose amount when the patient is receiving concomitant administration of a CYP3A inhibitor, wherein said original OD dose amount is selected from 900 milligrams (mg) per day and 1200 mg per day of said GRA, and said adjusted OD dose amount is 600 mg per day of said GRA.

Claim 28. A method of controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome, wherein said patient is taking a once- daily (OD) dose of mifepristone, said OD dose having an OD dose amount of 900 milligrams (mg) or 1200 mg mifepristone, comprising reducing the OD amount of mifepristone to provide a reduced OD dose of 600 milligrams (mg) mifepristone, and administering a said reduced OD dose of 600 mg mifepristone when the patient is receiving concomitant administration of a CYP3A inhibitor.

Prior art

The Korlym™ package insert teaches that Korlym™ (mifepristone) is a cortisol receptor blocker indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery. See package insert, "Indications and Usage" at page 1. The amount of mifepristone is *adjusted based on clinical response and tolerability*. See package insert, "Dosage and Administration" at page 1. The dose may be increased in 300 mg increments to a maximum of 1200 mg. See Id. In a study for treating Cushing's syndrome, the dose of mifepristone was increased from 300 mg to 600 mg, then to 900 mg for patients under 60kg or 1200 mg for patients over 60 kg based on clinical tolerance and clinical response. See

paragraph bridging pages 15 and 16. "Medications that inhibit CYP3A could increase plasma mifepristone concentrations and dose reduction of mifepristone *may* be required". See package insert, 7.2 CYP3A Inhibitors at page 9. Mifepristone should be used with caution in patients taking ketoconazole and other strong inhibitors (e.g., itraconazole, nefazodone, ritonavir, etc.) of CYP3A. See package insert, "5.6 Use of Strong CYP3A Inhibitors" at page 6. The insert teaches Mifepristone should be used in combination with strong CYP3A inhibitors only when necessary, and in such cases the dose should be limited to 300 mg per day. See Id.

While the Korlym™ (mifepristone) package insert teaches the use of mifepristone for the treatment of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome and further teaches the treatment of patients with Cushing's syndrome with 300 mg, 600 mg and 1200 mg mifepristone, it *does not expressly teach the patient receiving an original dosage that is subsequently decreased by at least 33%*. However, the package insert further teaches mifepristone should be used in combination with strong CYP3A inhibitors, such as ketoconazole, only when necessary, and in such cases the dose should be limited to 300 mg per day. Ulmann teaches that less than 40 or less than 20 mg/kg/day of mifepristone (and an inhibitor of cortisol synthesis such as ketoconazole, mitotane, metyrapone, aminoglutethimide, or fluconazole may be used to treat Cushing syndrome). See [0006], [0052]-[0054].

The claimed invention as a whole would have been prima facie obvious to one of ordinary skill before the effective filing date because both references teach the use of mifepristone for treating Cushing's syndrome. Both references also teach that ketoconazole can be combined with mifepristone, where Ulmann more specifically teaches that the combination of mifepristone and ketoconazole is useful for treating Cushing's syndrome.

One of ordinary skill in the art would have found it obvious to treat hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome with a composition containing mifepristone and ketoconazole. The artisan would have understood that both mifepristone and ketoconazole are taught to be used for treating Cushing's diseases and may be combined for that purpose (Ulmann). When combined, the artisan would have further recognized that a "reduction of mifepristone *may be required"*. Thus, if the Cushing's patient is treated with 1200 mg or 900 mg as disclosed by the package insert and it is found to be beneficial to combine with ketoconazole, then the artisan would have understood that the concentration of mifepristone may be adjusted by 300 mg increments and as tolerated (see package insert). For example, from 900 to 600 mg. Accordingly, the claimed invention as a whole would have been prima facie obvious to one of ordinary skill before the effective filing date.

Claim 2 depends from Claim 1, wherein GRA said is mifepristone; and said CYP3A inhibitor is a strong CYP3A inhibitor. These are clearly met as outlined above. Claim 3 depends from Claim 1, wherein said adjusted OD dose is 600 mg per day of said GRA after upwardly titrating the adjusted OD dose amount from 300 mg per day up to 600 mg per day of said GRA. The package insert provides clear guidance that the concentration of mifepristone should be adjusted as tolerated by the patient and further state that when mifepristone is combined with a strong CYP3A inhibitor such as ketoconazole, the amount of mifepristone may be adjusted and more particularly adjusted to 300 mg. While the prior art does not specifically lower mifepristone dosage to 300 mg and titrating it up to 600 mg, one of ordinary skill in the art would have understood that while lowering it to 300mg is the more preferred dose of mifepristone when combine with ketoconazole, the artisan would have recognized that the dose should be adjusted as

tolerated while considering the benefits and costs for using the combination of drugs for treatment. The insert teaches that adjusting the amount of mifepristone encompasses titrated by 300 mg. See 2.1 Adult Dosage at p. 3. Decisions about dose increases are based on clinical assessment of tolerability and degree of improvement in Cushing's syndrome manifestations. See Id. Claims 11 and 12 are similar to Claims 2 and 3 but depend from Claim 10 and are prima facie obvious for similar reasons. The same is true for Claims 20 and 21, which depend from Claim 19.

Claims 4 and 6 depend from Claims 3 while Claim 5 depends from Claim 1, wherein said GRA is mifepristone and said CYP3A inhibitor is a strong CYP3A inhibitor. Both Ulmann and the package insert teach the combination use of mifepristone and ketoconazole, whereas Ulmann specifically teaches their combination for treating Cushing's disease. Claims 13 and 15 depend from Claim 12 and Claim 14 depends from Claim 10 and are prima facie obvious for similar reasons. The same is true for Claims 22 and 24, which depend from Claims 21 and Claim 23 which depends from 19.

Claims 7-9 depend from Claims 1, 4, and 2, respectively, wherein said CYP3A inhibitor is ketoconazole. Claims 16-18 depend from Claims 10, 13 and 11, respectively, wherein said CYP3A inhibitor is ketoconazole. These claims are rendered prima facie obvious as outlined for Claims 4-6 and 13-15 above. The same is true for Claims 25-27 and 29, which depend from Claims 19, 22, 20 and 28, respectively.

Claim 30 depends from Claim 29, wherein said reduced OD dose of 600 mg mifepristone per day is titrated up to 600 mg mifepristone per day at least two days after administering at least

two reduced OD doses of 300 mg mifepristone per day. As outlined above, the package insert teaches that the adjustment of dose of mifepristone based on clinical tolerance and clinical response. Thus, one of ordinary skill in the art would have understood that while lowering it to 300mg is the more preferred dose of mifepristone when combine with ketoconazole, the artisan would have recognized that the dose should be adjusted as tolerated while considering the benefits and costs for using the combination of drugs for treatment. The increases in dose may by once every 2-4 weeks. See 2.1 Adult Dosage at p. 3.

Response to arguments

Applicant argues that the insert teaches that the dose of mifepristone should be limited to 300 mg per day when in combination with a strong CYP3A inhibitor such as ketoconazole. This is not persuasive because, while it is suggested that 300 mg mifepristone is preferable while the patient is taking a strong CYP3A inhibitor, the insert further teaches that the concentration of mifepristone should be adjusted as tolerated by the patient. One of ordinary skill in the art would have understood that while lowering it to 300 mg is suggested when combined with ketoconazole, the artisan would have recognized that the dose should be adjusted as tolerated while considering the benefits and costs for using the combination of drugs for treatment. The insert teaches that adjusting the amount of mifepristone encompasses titrating upwardly by 300 mg. See 2.1 Adult Dosage at p. 3. Decisions about dose increases are based on clinical assessment of tolerability and degree of improvement in Cushing's syndrome manifestations. See Id. Thus the artisan would have found it obvious to lower concentrations of mifepristone to 300 when the patient is also administered a strong CYP3A inhibitor and later increasing to 600 mg depending on several other

factors including clinical assessment of tolerability and degree of improvement in Cushing's syndrome manifestations.

Applicant asserts that the invention proves the prior art incorrect because the prior art would have led one of ordinary skill in the art to expect at least a 5-fold increase (e.g., 11-fold, 7-fold, 6-fold and 14-fold increases) in plasma levels of drugs when administered with a strong CYP3A inhibitor, whereas the current invention found that mifepristone only slightly increased by 28% when administered with ketoconazole. However, it is noted that the independent claims are not drawn to mifepristone or ketoconazole. Thus, any alleged unexpected results obtained using these two drugs are not commensurate in scope with claims that do not require them. Moreover, others have already demonstrated that ketoconazole only increased the AUC of drugs less than 5-folds. Indeed, coadministration of ritonavir with ketoconazole resulted in a 3.4-fold increase in the ketoconazole AUC but only an *18%* increase in ritonavir[1] AUC, which is lower than the 29% obtained by combing mifepristone and ketoconazole. See Kaeser et al. (ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2009, p. 609–614). Kaeser also teaches that others previously reported the increase in the saquinavir AUC by 37% and the ritonavir AUC by 29% when combined with ketoconazole. See p. 613, right col. Kaeser further teaches that the changes in AUC may be due to concentrations of drugs used. See Id. Thus, it would appear that finding that a strong CYP3A inhibitor increases the AUC of a coadministered drug by less than 5-fold would not have been surprising to one of ordinary skill in the art. As such, the declarant's arguments in the Belanoff declarations are not found to be persuasive.

[1] Ritonavir is metabolized by CYP3A. Thus, the strong inhibitor of CYP3A, ketoconazole, does not necessarily lead to 5-fold increases in coadministered drugs, including those known to be metabolized by CYP3A. (See Kumar et al. The Journal of Pharmacology and Experimental Therapeutics. Vol. 277, No. 1:423-431, 1996. See Abstract.)

Applicant argues that the Ulmann references teaches away from once a day dosing of mifepristone because the reference warns that once a day dosing "triggers a massive secretion of cortisol…leading to hypercortisolism" (par. [0008] of Ulmann). This is not persuasive because the insert teaches once a day dosing. Furthermore, Ulmann teaches that mifepristone may be administered at least twice a day or with an extended release. See abstract of Ulmann. Clearly, Ulmann teaches the extended-release compositions as an alternative to the at least twice a day composition, which clearly suggests once a day dosing.

While Applicant may attack Ulmann separately as not teaching or suggesting the claimed doses or adjusting the doses taught by Ulmann, it is noted that the rejection is an obviousness rejection over a combination of references. The insert clearly teaches adjusting the doses of mifepristone.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRIS E SIMMONS whose telephone number is (571)272-9065. The examiner can normally be reached on M-F: 8-4:30p.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571)272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CHRIS SIMMONS/
Examiner, Art Unit 1629

/RACHAEL E BREDEFELD/
Primary Examiner, Art Unit 1611

Notice of References Cited	Application/Control No. 15/627,359	Applicant(s)/Patent Under Reexamination Belanoff, Joseph K.	
	Examiner CHRIS E SIMMONS	Art Unit 1629	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
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	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Kaeser et al. (ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2009, p. 609–614). (Year: 2009)
	V	Kumar et al. The Journal of Pharmacology and Experimental Therapeutics. Vol. 277, No. 1:423-431, 1996. See Abstract. (Year: 1996)
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/627,359	Belanoff, Joseph K.
	Examiner	Art Unit
	CHRIS E SIMMONS	1629

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST, Inventor search	9/17/2017	CS
Google :"mifepristone adjusting dosage";"mifepristone CYP450 3A inhibitors is necessary, the dose should be limited to 300 mg per day"	9/17/2017	CS
EAST, Inventor search		
Google "ritinovir metabolism"	05/29/2018	CS

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S13	1	("20100261693").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/05/28 23:47
S14	11	(("CORCEPT") near3 ("THERAPEUTICS") near3 ("INC")).AANM.	USPAT	AND	OFF	2018/05/28 23:47
S15	18	(("BELANOFF") near3 ("Joseph")).INV.	USPAT	AND	OFF	2018/05/28 23:47
S16	8907	mifepristone	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/05/28 23:47
S17	24527	ketoconazole	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/05/28 23:47
S18	28	S15 or S14	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/05/28 23:47
S19	8	S18 S16 S17	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/05/28 23:47
S20	49	(("BELANOFF") near3 ("Joseph")).INV.	US-PGPUB; USPAT; USOCR	AND	OFF	2018/05/28 23:47
S21	332	(("CORCEPT") near3 ("THERAPEUTICS") near3 ("INC")).AANM.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/05/28 23:47
S22	372	S20 or S21	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/05/28 23:47
S23	24527	ketoconazole	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/05/28 23:47
S24	1521	S23 cushing	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/05/28 23:47
S25	16	S23 cushing.ti.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/05/28 23:47

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PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15/627,359
	Filing Date	June 19, 2017
	First Named Inventor	Joseph K. Belanoff
	Art Unit	1629
	Examiner Name	Chris E Simmons
	Attorney Docket Number	085178-1053027-011410US

U.S. PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code [1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

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Examiner Initial*	Cite No	Publication Number	Kind Code [1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/C.E.S/	C1	20170281651	A1	Oct 5, 2017	BELANOFF	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15627359
Filing Date	2017-06-19
First Named Inventor	Joseph K. Belanoff
Art Unit	1629
Examiner Name	Chris E. SIMMONS
Attorney Docket Number	085178-1053027-011410US

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Art Unit	1629
Examiner Name	Chris E. SIMMONS
Attorney Docket Number	085178-1053027-011410US

/C.E.S/	1	Greenblatt et al. "Ritonavir is the best alternative to ketoconazole as an index inhibitor of cytochrome P450-3A in drug-drug interaction studies," Brit. J. Clin. Pharmacol. 80(3):342-350 (2015))
/C.E.S/	2	"Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications Guidance for Industry" dated October 2017 https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093606.htm (accessed December 11, 2017)
/C.E.S/	3	"Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers" https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm (FDA website (cached), accessed December 8, 2017)
/C.E.S/	4	Chapter 1, "Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, and Elimination", Benet LZ et al., in The Pharmacological Basis of Therapeutics, Eighth Edition, Pergamon Press, Elmsford, New York, USA, 1990, pages 3-32
/C.E.S/	5	U.S. 15/627,368, final Office action issued December 5, 2017 for U.S. Application entitled "Concomitant Administration of Glucocorticoid Receptor Modulators and CYP3A or Steroidogenesis Inhibitors", filed June 19, 2017; inventor J. Belanoff, Applicant: Corcept Therapeutics; published as US 2017-0281651 A1.

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Examiner Signature	/CHRIS E SIMMONS/	Date Considered	05/28/2018

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Art Unit	1629
Examiner Name	Chris E. SIMMONS
Attorney Docket Number	085178-1053027-011410US

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☒ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/James A. Fox/	Date (YYYY-MM-DD)	2017-12-15
Name/Print	James A. Fox	Registration Number	38455

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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Request For Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	15/627,359
Filing Date	June 19, 2017
First Named Inventor	Joseph K. Belanoff
Art Unit	1629
Examiner Name	Chris E. Simmons
Attorney Docket Number	085178-1053027-011410US

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 C.F.R. 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
ii. ☐ Other _____

b. . ☒ Enclosed

i. ☒ Amendment/Reply
ii ☐ Affidavit(s)/Declaration(s)
iii. ☐ Information Disclosure Statement (IDS)
iv. ☒ Other 132 Declarations with CVs and Exhibits 2-8

2. Miscellaneous

a. ☐ Suspension of action on the above-identified application is requested under 37 C.F.R. 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 C.F.R. 1.17(i) required)

b. ☐ Other _____

3. Fees The RCE fee under 37 C.F.R. 1.17(e) is required by 37 C.F.R. 1.114 when the RCE is filed.

a. ☒ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 20-1430.

i. ☒ RCE fee required under 37 C.F.R. 1.17(e)
ii. ☐ Extension of time fee (37 C.F.R. 1.136 and 1.17)
iii. ☐ Other _____

b. ☐ Check in the amount of $ _____ enclosed

c. ☒ Payment by credit card (Form PTO-2038 enclosed)

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SIGNATURE OF APPLICANT, ATTORNEY OR AGENT REQUIRED			
Signature	/Kenneth A. Weber/	Date	July 18, 2018
Name (Print /Type)	Kenneth A. Weber	Registration No.	31,677

CERTIFICATE OF MAILING OR TRANSMISSION			
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.			
Signature	/Jo Ann Honcik Dallara/		
Name (Print /Type)	Jo Ann Honcik Dallara	Date	July 18, 2018

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Electronic Patent Application Fee Transmittal

Application Number:	15627359
Filing Date:	19-Jun-2017
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Filer:	Kenneth A. Weber/Jo Ann Honcik Dallara
Attorney Docket Number:	085178-1053027-011410US

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
RCE- 1ST REQUEST	2801	1	650	650
		Total in USD ($)		**650**

Electronic Acknowledgement Receipt

EFS ID:	33217887
Application Number:	15627359
International Application Number:	
Confirmation Number:	2957
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	144579
Filer:	Kenneth A. Weber/Jo Ann Honcik Dallara
Filer Authorized By:	Kenneth A. Weber
Attorney Docket Number:	085178-1053027-011410US
Receipt Date:	18-JUL-2018
Filing Date:	19-JUN-2017
Time Stamp:	16:58:47
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$650
RAM confirmation Number	071918INTEFSW16595800
Deposit Account	201430
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The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		AMDAF_1053027.pdf	362136 62afab57386faab0199a9d91598143aa2d41d097	yes	22
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment Submitted/Entered with Filing of CPA/RCE		1	1	
	Claims		2	6	
	Applicant Arguments/Remarks Made in an Amendment		7	22	
Warnings:					
Information:					
2	Affidavit-traversing rejectns or objectns rule 132	132Decls_Moraitis_Yau_Pearson_withCVs_1053027.pdf	8704495 306854a7d810e137d53418d27f938e74442431ad	no	95
Warnings:					
Information:					
3	Affidavit-traversing rejectns or objectns rule 132	Exhibits2-8.pdf	7930779 f48a51428a6d53d1bb7e2e258047a0a1859c406f	no	131
Warnings:					
Information:					
4	Request for Continued Examination (RCE)	RCE.pdf	147727 607f9f460765043e876ada5d66c293819f8fb9b9	no	1
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					

5	Fee Worksheet (SB06)	fee-info.pdf	31040 cf957617cc836fe6f480eb3c6d5a0d5d975ca0a0	no	2

Warnings:	
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on July 18, 2018.

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Jo Ann Honcik Dallara/
Jo Ann Honcik Dallara

PATENT
Attorney Docket No.: 085178-1053027-011410US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Joseph K. Belanoff

Application No.: 15/627,359

Filed: June 19, 2017

For: CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS

Customer No.: 144579

Confirmation No.: 2957

Examiner: Chris E. Simmons

Technology Center/Art Unit: 1629

AMENDMENT UNDER 37 C.F.R. § 1.116
EXPEDITED PROCEDURE

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

In response to the Final Office Action mailed June 12, 2018 in the above-referenced application, please enter the following amendments and consider the following remarks. A Request for Continued Examination is being filed concurrently herewith.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 7 of this paper.

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (Currently amended) A method of treating Cushing' s syndrome in a patient who is taking a once-daily (OD) dose of mifepristone ~~a glucocorticoid receptor antagonist (GRA)~~, said OD dose having an original OD dose amount of mifepristone ~~said GRA~~, comprising reducing the amount of the OD dose from said original OD dose amount to an adjusted OD dose amount that is at least 33% less than said original OD dose amount when the patient is receiving concomitant administration of a CYP3A inhibitor, wherein said original OD dose amount is ~~selected from~~ 900 milligrams (mg) per day ~~and~~ or 1200 mg per day of mifepristone ~~said GRA~~, and said adjusted OD dose amount is 600 mg per day of mifepristone ~~said GRA~~.

2. (Currently amended) The method of claim 1, wherein ~~said GRA is mifepristone, and~~ said CYP3A inhibitor is a strong CYP3A inhibitor.

3. (Currently amended) The method of claim 1, wherein said adjusted OD dose is 600 mg per day of mifepristone ~~said GRA~~, after upwardly titrating the adjusted OD dose amount from 300 mg per day up to 600 mg per day of mifepristone ~~said GRA~~.

4. (Currently amended) The method of claim 3, wherein ~~said GRA is mifepristone and~~ said CYP3A inhibitor is a strong CYP3A inhibitor.

5. (Currently Amended) The method of claim 1, wherein ~~said GRA is mifepristone and~~ said CYP3A inhibitor is selected from the group consisting of ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan. lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole.

6. (Currently amended) The method of claim 3, wherein ~~said GRA is mifepristone and~~ said CYP3A inhibitor is selected from the group consisting of ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan. lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole.

7. (original) The method of claim 1, wherein said CYP3A inhibitor is ketoconazole.

8. (original) The method of claim 4, wherein said CYP3A inhibitor is ketoconazole.

9. (Previously presented) The method of claim 2, wherein said CYP3A inhibitor is ketoconazole.

10. (Currently amended) A method of treating symptoms associated with elevated cortisol levels in a patient who is taking a once-daily (OD) dose of mifepristone ~~a glucocorticoid receptor antagonist (GRA)~~, said OD dose having an original OD dose amount of mifepristone ~~said GRA~~, comprising reducing the amount of the OD dose from said original OD dose amount to an adjusted OD dose amount that is at least 33% less than said original OD dose amount when the patient is receiving concomitant administration of a CYP3A inhibitor, wherein said original OD dose amount is ~~selected from~~ 900 milligrams (mg) per day ~~and~~ or 1200 mg per day of mifepristone ~~said GRA~~, and said adjusted OD dose amount is 600 mg per day of mifepristone ~~said GRA~~.

11. (Currently amended) The method of claim 10, wherein ~~said GRA is mifepristone and~~ said CYP3A inhibitor is a strong CYP3A inhibitor.

12. (Currently amended) The method of claim 10, wherein said adjusted OD dose amount is 600 mg per day of mifepristone ~~said GRA~~, after upwardly titrating the adjusted OD dose amount from 300 mg per day up to 600 mg per day of mifepristone ~~said GRA~~.

13. (Currently amended) The method of claim 12, wherein ~~said GRA is mifepristone and~~ said CYP3A inhibitor is a strong CYP3A inhibitor.

14. (Currently amended) The method of claim 10, wherein ~~said GRA is mifepristone and~~ said CYP3A inhibitor is selected from the group consisting of ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole.

15. (Currently amended) The method of claim 12, wherein ~~said GRA is mifepristone and~~ said CYP3A inhibitor is selected from the group consisting of ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole.

16. (Previously presented) The method of claim 10, wherein said CYP3A inhibitor is ketoconazole.

17. (Previously presented) The method of claim 13, wherein said CYP3A inhibitor is ketoconazole.

18. (Previously presented) The method of claim 11, wherein said CYP3A inhibitor is ketoconazole.

19. (Currently amended) A method of controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome who is taking a once-daily (OD) dose of mifepristone ~~a glucocorticoid receptor antagonist (GRA)~~, said OD dose having an original OD dose amount of mifepristone ~~said GRA~~, comprising reducing the amount of the OD dose from said original OD dose amount to an adjusted OD dose amount that is at least 33% less than said original OD dose amount when the patient is receiving concomitant administration of a

CYP3A inhibitor, wherein said original OD dose amount is ~~selected from~~ 900 milligrams (mg) per day ~~and~~ or 1200 mg per day of mifepristone ~~said GRA~~, and said adjusted OD dose amount is 600 mg per day of mifepristone ~~said GRA~~.

20. (Currently amended) The method of claim 19, wherein ~~said GRA is mifepristone and~~ said CYP3A inhibitor is a strong CYP3A inhibitor.

21. (Currently amended) The method of claim 19, wherein said adjusted OD dose is 600 mg per day of mifepristone ~~said GRA~~ after upwardly titrating the adjusted OD dose amount from 300 mg per day up to 600 mg per day of mifepristone ~~said GRA~~.

22. (Currently amended) The method of claim 21, wherein said ~~GRA is mifepristone and said~~ CYP3A inhibitor is a strong CYP3A inhibitor.

23. (Currently amended) The method of claim 19 wherein ~~said GRA is mifepristone and~~ said CYP3A inhibitor is selected from the group consisting of ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole.

24. (Currently amended) The method of claim 21, wherein ~~said GRA is mifepristone and~~ said CYP3A inhibitor is selected from the group consisting of ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saguinavir, telaprevir, telithromycin, and voriconazole.

25. (original) The method of claim 19, wherein said CYP3A inhibitor is ketoconazole.

26. (original) The method of claim 22, wherein said CYP3A inhibitor is ketoconazole.

27. (Previously presented) The method of claim 20, wherein said CYP3A inhibitor is

ketoconazole.

28. (Previously presented) A method of controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome, wherein said patient is taking a once daily (OD) dose of mifepristone, said OD dose having an OD dose amount of 900 milligrams (mg) or 1200 mg mifepristone, comprising reducing the OD amount of mifepristone to provide a reduced OD dose of 600 mg mifepristone, and administering a said reduced OD dose of 600 milligrams (mg) mifepristone when the patient is receiving concomitant administration of a CYP3A inhibitor.

29. (original) The method of claim 28, wherein said CYP3A inhibitor is ketoconazole.

30. (Previously presented) The method of claim 29, wherein said reduced OD dose of 600 mg mifepristone per day is titrated up to 600 mg mifepristone per day at least two days after administering at least two reduced OD doses of 300 mg mifepristone per day.

REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 1-30 will be pending in this application. Claims 1-6, 10-15 and 19-24 have been amended, No claims have been canceled, or newly added. No new matter is added. The claims have been amended to conform to conventional Markush claim language and to limit the claim scope from GRAs to mifepristone.

Based on the following remarks, Applicant respectfully requests reconsideration and allowance of the pending claims.

The currently pending claims of the subject application reflect the important discovery that mifepristone can be combined with strong CYP3A inhibitors and safely dosed at levels that are within recognized therapeutically effective dose ranges. This discover was contrary to the teachings of the prior art, which included an FDA warning not to exceed 300 mg per day of mifepristone when combined with CYP3A inhibitors. The FDA warning recommended a dose of mifepristone having no therapeutic benefit to 87% of the patients with Cushing's syndrome in the absence of CYP3A inhibitors and of unknown benefit to those patients when combined with CYP3A inhibitors.

DOUBLE PATENTING

The Examiner is reminded the Examiner Barbara Badio is currently examining a related application, USSN 15/627,368 ['368] application. A provisional Terminal Disclaimer was filed in the '368 application. The Examiner may wish to consider the necessity of a second Terminal Disclaimer for non-statutory double patenting in view of co-pending application No. 15/627,368.

35 USC §103

The pending claims have been rejected as obvious over the 2012 FDA approved Package Insert for Korlym® (mifepristone) in view of a published US patent application, Ulmann 2010/0261693. According to the Examiner, the Korlym® Package Insert teaches the need to

titrate the mifepristone dosage to provide optimal benefit to patients and Ulmann teaches the combination of mifepristone and ketoconazole. The Examiner wrote on page 8 of the final Office Action:

> Applicant argues that the insert teaches that the dose of mifepristone should be limited to 300 mg per day when in combination with a strong CYP3A inhibitor such as ketoconazole. This is not persuasive because, while it is suggested that 300 mg mifepristone is preferable while the patient is taking a strong CYP3A inhibitor, the insert further teaches that the concentration of mifepristone should be adjusted as tolerated by the patient. One of ordinary skill in the art would have understood that while lowering it to 300 mg is suggested when combined with ketoconazole, the artisan would have recognized that the dose should be adjusted as tolerated while considering the benefits and costs for using the combination of drugs for treatment. The insert teaches that adjusting the amount of mifepristone encompasses titrating upwardly by 300 mg. See 2.1 Adult Dosage at p. 3.

As the Examiner knows, once a *prima facie* case of obviousness is presented, the burden shifts to the patent applicant to rebut the rejection by showing that the *prima facie* case of obviousness is legally insufficient or by a showing of surprising results. Applicant will do both. Applicant will first present prior art that expressly teaches away from the claimed doses by at least two-fold and that the interpretation of the FDA 2012 Package Insert as a mere suggestion is an improper reading of the prior art. The prior art references collectively present a classic story of teaching away that legally rebuts any *prima facie* case of obviousness based on drug optimization law. Applicant will further explain that the prior art suggestion of 300 mg/day was a dose unlikely to provide any therapeutic benefit to the great majority of patients, which means the pending claim provides a dose that is a difference in kind rather than of a degree. Finally, applicant presents three declarations by experts who attest to the unpredictable nature and surprising advantages of the claimed invention.

1. TEACHING AWAY

A *prima facie* case of obviousness can be effectively rebutted by prior art that teaches away from the claimed invention. Providing evidence of an express teaching away is one of the most persuasive arguments with which to rebut a rejection based on a *prima facie* case of

obviousness. See MPEP §2145 Consideration of Applicant's Rebuttal Arguments [R-08.2012] where the MPEP states:

> **1. The Nature of the Teaching Is Highly Relevant**
>
> A prior art reference that "teaches away" from the claimed invention is a **significant** factor to be considered in determining obviousness; (Emphasis added)
>
> **3. Proceeding Contrary to Accepted Wisdom Is Evidence of Nonobviousness**
>
> The **totality of the prior art must be considered**, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986) (Emphasis added)

The relevant decisional law upon which the MPEP is based is also clear. When rejecting claims as obvious, the patent examiner cannot ignore references that teach away and must consider all arguments timely submitted. See *In re Lunsford*, 148 USPQ 721 CCPA (1965) where the court wrote:

> The provisions of section 103 must be followed realistically to develop the factual background against which the section 103 determination must be made. **All of the facts must be considered and it is not realistic within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.** (Emphasis added)

This is made even more clear in *Akzo v EI duPONT*, 1 USPQ 2d 1241 (Fed. Cir. 1987) where the court stated:

> As the ALJ recognized, prior art references before the tribunal must be read as a whole and consideration must be given where the references diverge and teach away from the claimed invention.

In the instant case, there are two prior art documents that expressly teach away from the doses of the subject claims. First the FDA mandated in 2012 that the Korlym® Package Insert expressly warn physicians to limit mifepristone dosing to 300 mg/day when combined with a CYP3A inhibitor. See Exhibit 3 of the three expert Declarations which reads as follows:

----------**DRUG INTERACTIONS**----------

• Drugs metabolized by CYP3A: Administer drugs that are metabolized by CYP3A at the lowest dose when used with Korlym (7.1).

• CYP3A inhibitors: Caution should be used when Korlym is used with strong CYP3A inhibitors. Limit mifepristone dose to 300 mg per day when used with strong CYP3A inhibitors (5.6, 7.2).

In an academic review article by Morgan and Laufgraben, 2013, *Pharmacotherapy*, Vol. 33(3):319-29 (Attachment A), the authors wrote:

> Because ketoconazole is readily available and has a mechanism of action distinct from that of mifepristone, the combination of mifepristone with ketoconazole is a logical choice and may have added benefit for the treatment of Cushing's syndrome. However, because ketoconazole is a CYP3A inhibitor, it can increase mifepristone concentrations and **the dose of mifepristone should not exceed 300 mg/day if used in combination with ketoconazole.** (Emphasis added)

Even Ulmann wrote in 2008 that less mifepristone was preferred when combined with a CYP3A inhibitor. At page 9, Ulmann wrote:

> Preferably the glucocorticoid receptor antagonist is mifepristone and the inhibitor of cortisol synthesis is mitotane, metyrapone, aminoglutethimide, fluconazole or ketoconazole.
>
> Preferably the daily dosage is less than about 40mg/kg/day, preferably less than about 20 mg/kg/day.
>
> The total daily amount of the glucocorticoid receptor antagonist administered may be advantageously inferior or equal to 800 mg, preferably inferior or equal to 600 mg, still preferably inferior or equal to 400 mg, still **more preferably inferior or equal to 300 mg.** (Emphasis added)

When viewed as a whole and interpreted by one of ordinary skill in the art, the only fair reading of these three references is that **a maximum dose of 300 mg per day or less mifepristone when combined with a CYP3A inhibitor is taught** and using more than this amount of mifepristone is expressly taught away.

EACH PRIOR ART REFERENCE IS TO BE GIVEN DUE WEIGHT AND CONSIDERATION

The Examiner is legally required to give due and fair consideration to the quality of the three references. A newspaper article should not be given the same weight as a peer reviewed journal article. See *In re Lundsford* above:

> All of the facts must be considered and it is not realistic within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the **full appreciation of what such reference fairly suggests to one of ordinary skill in the art.** (Emphasis added)

In the instant situation, applicant has presented two references for consideration by the Examiner. One is the FDA approved label dated 2012 that forms the basis for *prima facie* case of obviousness. The other is an article written in a peer reviewed journal dated 2013. Applicant notes that, as attested to in the Declarations submitted with this Response, those of skill in the art attach great weight to the recommendations and warnings in an FDA label. Peer-reviewed articles in respected publications, such as the one cited above, also receive serious consideration by skilled physicians. The Examiner is of the view that the express statements in the FDA approved label are mere suggestions to physicians. The Examiner wrote at pages 6 - 8 of the final Office Action:

> One of ordinary skill in the art would have found it obvious to treat hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome with a composition containing mifepristone and ketoconazole. The artisan would have understood that both mifepristone and ketoconazole are taught to be used for treating Cushing' s diseases and may be combined for that purpose (Ulmann). When combined, the artisan would have further recognized that a "reduction of mifepristone may be required". Thus, if the Cushing' s patient is treated with 1200 mg or 900 mg as disclosed by the package insert and it is found to be beneficial to combine with ketoconazole, then **the artisan would have understood that the concentration of mifepristone may be adjusted by 300 mg increments and as tolerated (see package insert).**
>
> While the prior art does not specifically lower mifepristone dosage to 300 mg and titrating it up to 600 mg, one of ordinary skill in the art would have understood that while lowering it to 300 mg is the more preferred dose of mifepristone when combine with ketoconazole, **the artisan would have recognized that the dose should be adjusted as tolerated while considering the benefits and costs for using the combination of drugs for treatment.**
>
> As outlined above, the package insert teaches that the adjustment of dose of mifepristone based on clinical tolerance and clinical

> response. Thus, one of ordinary skill in the art would have understood that while lowering it to 300 mg is the more preferred dose of mifepristone when combine with ketoconazole, **the artisan would have recognized that the dose should be adjusted as tolerated while considering the benefits and costs for using the combination of drugs for treatment.**

In the above text, the Examiner has conflated the general instructions of titration with express statements in the "Warnings and Precautions" section of the label. More specifically, the Package Insert states not to exceed 300 mg/day when mifepristone is combined with a CYP3A inhibitor. The purpose of the "Warnings and Precautions" section of the label is to provide important, safety-related exceptions and limitations to those general instructions.

As explained by experienced clinicians, Drs. Moraitis and Yau in their supplemental Rule 132 Declarations both dated July 16, 2018, FDA labels are recommendations for good medical practice based on the best available evidence. Although it is not illegal for physicians to deviate from the instructions in a medications label, by doing so they expose their patients to medical risk and themselves to significant legal liability. In practice, physicians often prescribe medications for unapproved uses; but, they do so at doses that are widely understood to be safe and effective. According to the declarants, physicians do not use drugs in contravention of the express warnings in a medication's FDA-mandated label. Korlym's label expressly instructs the physician to titrate dosing to optimize patient benefit **except when mifepristone is combined with a CYP3A inhibitor ("Limit mifepristone dose to 300 mg per day when used with strong CYP3A inhibitors")**. To interpret the label as general instructions to titrate mifepristone dosing under *any* conditions is to ignore its plain meaning.

In view of the above remarks including the additional prior art of Morgan expressly teaching dosing of mifepristone at 300 mg/day when combined with a CYP3A inhibitor, applicant respectfully submits that the *prima facie* case of obviousness rejecting the pending claims has been fully rebutted. Neither the label nor Ulmann motivate the person of skill to expect a mifepristone dose of greater than 300 mg/day to be anything other than a toxic dose. Finally, the fact that Kaeser (2009) teaches that ketoconazole did not cause a dramatic increase in saquinavir, a drug unrelated, to mifepristone does not lend strength to the Examiner's position regarding how a physician would interpret the Korlym® Package Insert.

2. A DIFFERENCE IN KIND

It is well settled law that when patent application claims present an invention of optimization that evidence of a *difference in kind* is a powerful argument in favor of non-obviousness. As stated in the MPEP at Section 2144.05 Obviousness of Similar and Overlapping Ranges, Amounts, and Proportions [R-08.2017]

> Applicants can rebut a prima facie case of obviousness by showing the criticality of the range. "The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. . . . In such a situation, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range." In reWoodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See also Minerals Separation, Ltd. v. Hyde, 242 U.S. 261, 271 (1916) ... In re Lilienfeld, 67 F.2d 920, 924 (CCPA 1933) **("It is well established that, while a change in the proportions of a combination shown to be old, such as is here involved, may be inventive, such changes must be critical as compared with the proportions used in the prior processes, producing a difference in kind rather than degree.").** [emphasis added]

In the instant facts, the FDA stated that the daily dose of mifepristone should not exceed 300 mg/day when combined with a CYP3A inhibitor. According to the seminal clinical study, the 300 mg/day dose is essentially non-therapeutic to the vast majority of the patients with Cushing's syndrome. The details of this clinical study were reported in Fleseriu (2012) which is Exhibit 7 of the three expert declarations. As explained in more detail below and in the declarations, only 13.3 % of the patients in the study responded to this low dose. The authors of Fleseriu wrote on page 2042, column 1:

> The most common doses among responders at wk 24/ET were 600 mg (40%) and 1200 mg (40%), followed by 300 mg (13.3%) and 900 mg (6.7%).

As explained below, optimal dosing of mifepristone is complicated by a steroid binding protein that is present in varying quantities in patients. The protein is α-1-acid glycoprotein (AAG, also known as orosomucoid). Preferential binding by AAG removes much of the free mifepristone in plasma before it can bind to GR and produce therapeutic benefit.

As Fleseriu described, for more than 85% of the patients with Cushing's syndrome, a daily dose of greater than 300 mgs of mifepristone is needed for therapeutic benefit. However, the FDA set a maximum dose of 300 mg/day when mifepristone is combined with a CYP3A inhibitor and they also required a second study in healthy people to ensure that the blood levels

of mifepristone would not rise to toxic levels even at 300 mg/day. The results of this second clinical study are the basis for the subject application.

Fortuitously and surprisingly, the combination of mifepristone at 300 mg/day and a CYP3A inhibitor (ketoconazole) did not result in toxic levels of mifepristone; instead, there was just a 28 - 38% increase in mifepristone (see, e.g., Table 3 of the present application). The FDA was expecting a significant increase and expected those patients taking the combination therapy to have much higher blood levels of mifepristone when administered with a strong CYP3A inhibitor such as ketoconazole.

The clinical results presented in the subject application convinced the FDA to authorize an amendment to the label permitting the maximum dose of mifepristone to be 600 mg/day with strong CYP3A inhibitors such as ketoconazole. At a 600 mg/day mifepristone dose with ketoconazole, the mifepristone level is well within the therapeutic range for mifepristone, and not in the toxic range. See Exhibit 8 of the Experts' Declarations.

Based on this information, applicant submits that the prior art dose and the claimed dose represent a difference in *kind* rather than degree. A 300 mg/day dose of mifepristone, even co-administered with a CYP3A inhibitor, would be too low to benefit the vast majority of Cushing's patients. By contrast, a 600 mg/day dose, when given with a strong CYP3A inhibitor, would benefit most patients. Applicant respectfully submits that the difference between a non-therapeutic dose and a therapeutic dose of mifepristone is an irreproachable example of a difference in kind and that the *prima facie* case of obviousness has been fully rebutted.

3. SURPRISING ADVANTAGES

(i) *The Law*.

Although applicant respectfully submits that the totality of the prior art discussed above is legally sufficient to rebut the *prima facie* case of obviousness, applicant presents three Rule 132 declarations from experts to evidence the surprising advantages of the pending claims. The Federal Circuit wrote in *In re Soni*, 34 U.S.P.Q.2D 1684 (Fed Cir. 1995):

> One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of "unexpected results,"

> i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward -- that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. The principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results.

Soni also provides us with the practical rules for proving surprising advantages:

> Consistent with the rule that all evidence of nonobviousness must be considered when assessing patentability, the PTO must consider comparative data in the specification in determining whether the claimed invention provides unexpected results. However, "it is well settled that unexpected results must be established by factual evidence. Mere argument or conclusory statements in the specification does not suffice." ("Mere lawyer's arguments and conclusory statements in the specification, unsupported[**12] by objective evidence, are insufficient to establish unexpected results."); ("Mere conclusory statements in the specification . . . are entitled to little weight when the Patent Office questions the efficacy of those statements.").

Having provided the legal framework for consideration of surprising results to traverse a *prima facie* case of obviousness, we now turn to the declaratory evidence presented by Drs. Andreas Moraitis, Hanford K.S. Yau and Paul Pearson. Drs. Moraitis and Yau are endocrinologists familiar with treating patients with Cushing's syndrome. Dr. Pearson is a Ph.D. with expertise in the pharmacology of mifepristone.

In summary, the declarants explain that doctors treating patients with Cushing's syndrome and following good medical practice will also have reason to treat their patients with drugs that are strong CYP3A inhibiters. For reasons explained in detail below and in the declarations, persons of skill in the art were informed by the prior art to expect that the combination of mifepristone at ordinarily effective doses with CYP3A inhibitors would have increased blood levels of mifepristone to toxic levels. In response to the expectation of toxicity, the prior art expressly taught a reduction in dose of mifepristone to 300 mg per day or less. As further explained in the declarations and below, doses of mifepristone at or below 300 mg per day, even in the presence of a strong CYP3A inhibitor, present serious questions of therapeutic

efficacy due to the presence of orosomucoid, a glycoprotein in blood that is capable of strongly binding mifepristone and rendering it unavailable to bind to its therapeutic target, GR.

In view of the accepted beliefs of those of skill in the art prior to the results disclosed in the present application, clinical studies would have to be conducted to determine if patients taking a combination of mifepristone and a CYP3A inhibitor such as ketoconazole would see any therapeutic benefit from the required low (300 mg/day) dose of mifepristone. Surprisingly and advantageously, the combination of ketoconazole and mifepristone did not lead to a multi-fold increase in blood concentration of mifepristone. This unexpected discovery persuaded the FDA in 2017 to amend its initial restrictions on mifepristone and approve the use of mifepristone at up to 600 mg/day when combined with CYP3A inhibitors. (See Exhibit 7 of the three expert declarations).

(ii) *Why Cushing's patients need combination therapy.*

The three declarants present a consistent explanation of the medical rationale behind the motivation or desire to treat a significant percentage of Cushing's patients with mifepristone and a CYP3A inhibiter. Patients with Cushing's syndrome patients are immune suppressed. They suffer from infections, depression and other medical conditions. They can and do benefit from the co-administration of mifepristone with other drugs, some of which are strong CYP3A inhibitors. In ¶ 6 of the three declarations, the experts explain that physicians would have avoided the use of CYP3A inhibiting drugs with Cushing's patients because the recommended maximum dose of mifepristone of 300 mg/day was less than half the average effective dose of about 800 mg/day for patients taking mifepristone.

(iii) *Combining CYP3A inhibitors and mifepristone was contraindicated by the FDA.*

As explained in the declarations, the combination of mifepristone with CYP3A inhibitors (exemplified by ketoconazole) gave rise to a serious concern about over-dosing with mifepristone. Mifepristone is known to be metabolized by the cytochrome P450 enzyme, CYP3A. Ketoconazole is known to be a powerful and selective inhibitor of CYP3A. When inhibitors of the CYP3A enzyme are combined with drugs *selectively* metabolized by that enzyme, toxic levels of the drugs can quickly develop. The phenomenon is unpredictable, because some drugs are selectively metabolized by CYP3A and others are metabolized by

multiple members of the P450 CYP family. If selectively metabolized by CYP3A, drug levels can increase to between 7 and 20 times the levels in the absence of the CYP3A inhibitor. The declarants call this phenomenon – when drug levels spike dramatically –the *Greenblatt effect* after one of the investigators who has studied this effect with different drugs. Mifepristone toxicity in the presence of ketoconazole was a serious concern to the FDA.

The FDA anticipated the desire of doctors to combine CYP3A inhibitors and mifepristone for their Cushing's patients. In the absence of sufficient clinical data, and with the understanding that the Greenblatt effect may result in toxic levels of mifepristone, the FDA required that the 2012 Package Insert place an upper limit on miferpristone of 300 mg/day when combined with a CYP3A inhibitor such as ketoconazole (See Dr. Moriatis's Declaration at ¶ 6 and Exhibit 3, Korlym 2012 label). In addition, the FDA further required Corcept to test for the Greenblatt effect in healthy adults. The FDA stated that "only a clinical trial (rather than a nonclinical or observational study) will be sufficient to characterize the effect of co-administration of strong CYP3A inhibitors on increasing mifepristone drug levels and to assess the potential for the known serious risks of severe hypokalemia and adrenal insufficiency". See Dr. Moraitis's Declaration at ¶6 and Exhibit 3, FDA Approval Letter for NDA 202107 (signed February 17, 2012). In this letter, the FDA mandated that Corcept study mifepristone levels in a supplemental clinical trial with persons exposed to strong CYP3A inhibitors.

(iv) Surprising Advantages

The results of the FDA mandated supplemental clinical study are presented in the subject patent application. Its results unexpectedly showed that the combination of mifepristone and ketoconazole (acting in this study, per FDA standard procedure, as a stand-in for all strong CYP3A inhibitors) did not result in dangerously high increases in mifepristone levels. In fact, levels of mifepristone increased by only between 28 and 38%.

As explained by the three declarants, the failure to observe the Greenblatt effect during the seminal clinical study was surprising, unpredictable and very advantageous to patients with Cushing's syndrome. In section 7(a) of each declaration, the experts present objective evidence that the Greenblatt effect is not a predictable phenomenon even as to steroidal drugs like mifepristone. Among the multiple examples of this unpredictability presented by the declarants,

there is an example with the steroidal drug eplerenone. Unlike mifepristone, eplerenone is one of the steroid-like drugs that exhibit the Greenblatt effect with a five-fold increase. Another steroidal drug, methylprednisolone, demonstrated a 134% increase when combined with ketoconazole (see pages 9-10 of the three Rule 132 declarations). As explained by the declarants, the impact of ketoconazole on the AUC and Cmax of specific drugs varies widely and unpredictably – even among drugs of the same class. Accordingly, the impact of CYP3A inhibitors on drug metabolism must be determined empirically on a drug-by-drug basis.

It should be noted that the Kaeser (2009) paper is not particularly relevant to the *prima facie* case of obviousness because Kaeser is an example of the unpredictability of the Greenblatt effect. The Examiner argues that Kaeser is an example of ketoconazole having little impact on blood levels of a drug and therefore would lead one of skill to conclude that a similar effect is expected when ketoconazole is co-administered to patients taking mifepristone. As remarked upon by the three experts in Section 7(a), Kaeser is indeed an example of when ketoconazole had little impact on blood levels of a different drug but this is far from representative of all drugs. The title of the Kaeser paper is "Drug-Drug Interaction Study of Ketoconazole **and Ritonavir-Boosted Saquinavir**. The reason that blood levels of saquinavir were unchanged in the Kaeser paper was likely due to the fact that the CYP3A enzyme was already fully inhibited or "boosted" by ritonavir. The Kaeser abstract reads:

> Saquinavir, a potent human immunodeficiency virus protease inhibitor, is extensively metabolized by CYP3A4. Saquinavir is coadministered with ritonavir, a strong CYP3A4 inhibitor, to boost its exposure. Ketoconazole is a potent CYP3A inhibitor.

Had the Greenblatt effect been observed in the study described in the subject application, the FDA-permitted dosing of mifepristone would have had to be reduced significantly below even the previously FDA-specified maximum dose of 300 mg, to perhaps 100 mg/day. As is explained below, at doses of 300 mg/day and less, there are serious questions of mifepristone's clinical efficacy.

In section 7(b) of the three Rule 132 Declarations, the doctors explain the great clinical value of the claimed invention. The discovery that the Greenblatt effect does not occur when mifepristone is combined with a CYP3A inhibitor allows patients with Cushing's syndrome to be

treated with mifepristone at proven therapeutic levels even when mifepristone is combined with CYP3A inhibitors. Had the Greenblatt effect been observed, the FDA would have required correspondingly low doses of mifepristone when administered with a CYP3A inhibitor. These low doses give rise to serious questions about therapeutic efficacy because effective dosing of mifepristone is not simply a linear adjustment of amount in response to increases in AUC and C_{max} values related to anticipated CYP3A inhibition.

According to the declarants, effective dosing of mifepristone requires achieving sufficient "free" (as opposed to "bound") amounts of mifepristone in the patient's blood. Mifepristone is very potently bound by α-1-acid glycoprotein (AAG, also known as orosomucoid). Preferential binding by AAG removes much of the free mifepristone in plasma before it can bind to GR and produce therapeutic benefit. The binding of mifepristone to AAG requires doctors to carefully titrate up the amount of mifepristone administered to each patient until the optimum dose is achieved. At higher doses of mifepristone, the binding capacity of AAG becomes saturated and free mifepristone is available to bind to its target, GR. At lower mifepristone doses, the quantity of AAG in a patient's blood becomes a determinative factor of mifepristone's therapeutic efficacy. Because the amount of AAG varies widely in patients, the therapeutic benefit of low mifepristone doses is difficult to predict.

The three declarants further state that the arithmetic average dose of mifepristone needed to effectively control Cushing's syndrome is just over 800 mg/day. The results of the seminal clinical study that led to the approval of mifepristone for the treatment of Cushing's syndrome were published by Fleseriu *et al.* (2012). Fleseriu is Exhibit 7 of the three Rule 132 declarations. As taught by Fleseriu, the number of responders at 300 mg/day was only 13.3%. The authors of Fleseriu wrote on page 2042, column 1:

> The most common doses among responders at wk 24/ET were 600 mg (40%) and 1200 mg (40%), followed by 300 mg (13.3%) and 900 mg (6.7%).

As explained by the declarants, these trial results show that the low doses of mifepristone recommended by the FDA in the presence of CYP3A inhibitors benefit very few patients (13.3%) – a result borne out by the broader patient population, where the average effective dose is more than 800 mg/day. The ineffectiveness of low mifepristone doses would be true even in

the presence of CYP3A inhibition, because AAG binding would render a low dose biologically unavailable in most patients.

Had the Greenblatt effect applied, determining the safe and effective dose levels of therapies combining mifepristone and CYP3A inhibitors would have required Corcept, the assignee of the subject application, to study the combination in patients at dose levels of mifepristone extending significantly lower than 300 mg/day – a dose that had been shown to be ineffective for the great majority of patients. As stated by the declarants in section 7(b),

> At a minimum, additional clinical studies would have had to be conducted to determine whether low doses of mifepristone in the presence of ketoconazole or other CYP3A inhibitor were clinically effective and safe. Because low levels of mifepristone of < 300 mg/day were known to be ineffective for the majority of patients with Cushing's syndrome, the therapeutic profile of mifepristone in patients would have had to be established for those patients in need of combination therapy. To do otherwise would have been medically unethical. Such studies would have cost tens of millions of dollars and delayed the availability of mifepristone for this patient group for 3-5 years.

Fortunately and surprisingly, the results presented in the subject application demonstrate that mifepristone is not subject to the Greenblatt effect. There is only about a 28 - 38% increase in blood levels of mifepristone in the presence of ketoconazole. This means that the claimed methods requiring a 33% reduction in the original mifepristone dose when administered in the presence of CYP3A inhibitors provide safe, effective, and nontoxic, levels of mifepristone. Surprisingly, the claimed methods provide mifepristone dose levels that are within the ranges approved by the FDA for patients not receiving a CYP3A inhibitor.

The FDA has recognized the value to patients of the study and methods presented in the subject application. In 2017, the FDA allowed the 2012 label to be revised to recommend a dose of mifepristone that is double the originally permitted dose (See Dr. Moriatis's Declaration -Exhibit 8). The revised label language reads as follows:

> • *Use of Strong CYP3A Inhibitors:* Concomitant use can increase mifepristone plasma levels. Use only when necessary and limit mifepristone dose to 600 mg (5.6).

Corcept expects the FDA to recommend a further increase in the recommended dose of Korylm® to 900 mg/day when combined with CYP3A inhibitors.

3. CLAIMS RECITING DOSING OPTIMIZATION SET FORTH A *PRIMA FACIE* CASE OF OBVIOUSNESS THAT IS REBUTTABLE UNDER LAW.

In view of the above remarks and the three Rule 132 declarations, applicant submits that the rejection of the pending claim over Ulmann has been fully traversed. The decisional case law sets forth optimization of drug dosing as establishing a *prima facie* case of obviousness. If the Examiner intends to maintain the rejection over the above remarks and declaratory evidence of Drs. Moraitis, Yau and Pearson without appropriate and objective rebuttal evidence, then the *prima facie* case of obviousness will have become effectively irrebuttable. As articulated by Judge Plager in his thoughtful concurrence in *In re Oetiker*, 24 USPQ 2d 1443 at 1447 (Fed. Cir. 1992), a *prima facie* case of obviousness is by definition rebuttable:

> Specifically, when obviousness is at issue, the examiner has the burden of persuasion and therefore the initial burden of production. Satisfying the initial burden of production and thus initially the burden of persuasion, constitutes the so-called prima facie showing. Once that burden is met, the applicant has the burden of production to demonstrate that the examiner's preliminary determination is incorrect. ... If, as a matter of law, the issue is in equipoise, the applicant is entitled to the patent.

In response to the *prima facie* case of obviousness presented by the Examiner, the applicant has, supported by the Declarations of Drs. Moraitis, Yau, and Pearson, presented superior prior art expressly teaching away from the invention and explained that the prior art-suggested dose limitations and the claimed doses and methods differ in kind and not degree. Together, these fully rebut the *prima facie* case of obviousness. When considered in combination with the three expert declarations providing objective evidence of the claimed invention's surprising advantages, applicant submits that he has fully overcome the *prima facie* case of obviousness presented by the Ulmann reference and the 2012 Korlym label in view of Kaeser.

CONCLUSION

In conclusion, applicant has presented prior art that expressly teaches that the highest recommended dose of mifepristone in the presence of a CYP3A inhibitor is **300 mg/day or less**. Applicant is claiming adjusted mifepristone doses of 600 mg per day and submits that the rejected claims are non-obvious because they run counter to the recommended suggestions

taught by the prior art. The prior art references present a classic story of teaching away and by themselves are legally sufficient to rebut the *prima facie* case of obviousness based on decisional law concerning optimization-type inventions. In addition, applicant has explained that the claimed dose of 600 mg/day represents a difference in kind rather than *optimization by degree*. Finally, applicant has presented three declarations by experts who attest with scientifically objective reasons to the surprising advantages of the claimed invention.

In view of the foregoing, Applicant believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Except for the issue fees payable under 37 C.F.R. § 1.18, the Director is authorized to charge any additional fees during pendency of this application, including any required extension of time fees, or credit any overpayment to Deposit Account Number 20-1430. This paragraph is intended to be a constructive petition for extension of time in accordance with 37 C.F.R. § 1.136(a)(3).

If the Examiner believes a telephone conference would expedite prosecution of this application, please contact the undersigned at (415) 576-0200 or KWeber@KilpatrickTownsend.com.

Respectfully submitted,

/Kenneth A. Weber/
Kenneth A. Weber
Registration No. 31,677

KILPATRICK TOWNSEND & STOCKTON LLP

Supplemental Rule 132 Declaration

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on June 28, 2018

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Jo Ann Honcik Dallara/
Jo Ann Honcik Dallara

PATENT
Attorney Docket No.: 085178-1053029-011420US
Client Ref. No.:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Confirmation No.: 3411
Joseph K. Belanoff	Examiner: Barbara P. Badio
Application No.: 15/627,368	Technology Center/Art Unit: 1628
Filed: June 19, 2017	
For: CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A OR STEROIDOGENESIS INHIBITORS	RULE 132 DECLARATION BY DR. ANDREAS MORAITIS
Customer No.: 144579	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

I, Dr. Andreas Moraitis, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true. The Exhibits (1-8) attached hereto are incorporated herein by reference.

2. I received a medical doctorate from the National and Kapodistrian University of Athens, Greece, in 2002, and received fellowship training in adult and reproductive endocrinology at the U.S. National Institutes of Health (2010-2012). I am a board certified in

internal medicine by the American Board of Internal Medicine and am board certified in endocrinology by the American Board of Endocrinology and Metabolism. I held the academic appointment of Assistant Professor, Endocrine Oncology, at the University of Michigan Medical School (2012-2014). I am presently employed Corcept Therapeutics, Inc. where I am Director of Clinical Development. I have treated Cushing's syndrome patients and I am familiar with modern medical treatments for patients with Cushing's syndrome. My *curriculum vitae* is attached as Exhibit 1.

3. I have read the subject application USSN 15/627,368, the outstanding non-final Office Action dated March 16, 2018 and the prior art reference cited by the Examiner (WO 2009/050136 (Ulmann). I understand that the Examiner believes the pending claims to be obvious over Ulmann.

The purpose of this declaration is to provide objective evidence of surprising advantages sufficient to traverse the outstanding rejection.

4. THE INVENTION

The pending claims recite a dosing regimen for treating Cushing's syndrome with a combination of mifepristone and a CYP3A inhibitor. The specifics of the claimed invention require that original amount of mifepristone in the absence of the CYP3A inhibitor be reduced by at least 25% to a dose that is greater than **800** mg/day when combined with the CYP3A inhibitor. This claim stands in contrast to the FDA original maximum dose of no greater than **300** mg/day when combined with ketoconazole, which is a strong CYP3A inhibitor that is often used to treat patients with Cushing's syndrome. Pending claim 1 reads:

> 1. A method of treating Cushing's syndrome in a patient who is taking a once daily (OD) dose of mifepristone comprising reducing the once-daily dose amount of said mifepristone administered to said patient from an original OD mifepristone dose amount to an adjusted OD mifepristone dose amount that is greater than 800 mg and is at least 25% less than said original OD mifepristone dose amount when the patient is receiving concomitant administration of a CYP3A inhibitor selected from ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole, cobicistat, danoprevir, elvitegravir indinavir, paritaprevir ombitasvir dasabuvir and troleandomycin.

The outstanding obviousness rejection is over Ulmann (WO 2009/0501136). Ulmann teaches the combination of glucocorticoid receptor antagonists (*eg.* mifepristone) and cortisol synthesis inhibitors (*eg.* ketoconazole) to treat patients with Cushing's syndrome. The Examiner finds the claimed invention to be *prima facie* obvious.

As discussed below, based on my clinical training and experience, I find the claimed invention to be unexpected and to provide advantages to patients with Cushing's syndrome and doctors treating them.

5. BACKGROUND

Cushing's syndrome is defined by the overproduction of cortisol. It is a life-threatening disorder typically caused by a tumor. The tumor either produces cortisol or adrenocorticotropic hormone (ACTH). ACTH causes the adrenal glands to produce cortisol. By binding to the glucocorticoid receptor (GR), cortisol performs many essential physiological functions. Cortisol also binds to the mineralocorticoid receptor (MR). Significant cortisol binding at MR occurs when cortisol levels are very high.

The abnormally high levels of cortisol in patients with Cushing's syndrome result in excessive activity at the GR, which causes the symptoms of Cushing's syndrome. These symptoms include hyperglycemia, hypertension, persistent infections, hypokalemia, bone loss, hirsutism, psychosis, depression, hirsutism and other adverse effects. The median life expectancy of untreated patients with severe Cushing's syndrome is approximately five years.

Treating patients with Cushing's syndrome presents complex clinical challenges. Surgery to remove the tumor that is secreting excess cortisol or ACTH is the preferred treatment but is successful in only 50 percent of patients. In the remaining 50 percent of patients, physicians use drugs to reduce cortisol activity.

Before the FDA's approval of mifepristone to treat Cushing's syndrome in 2012, the standard of care was to administer cortisol synthesis inhibitors such as ketoconazole. An undesired side effect of ketoconazole is to strongly inhibit CYP3A. CYP3A is a family of enzymes responsible for the metabolism (i.e., breakdown and clearance) of mifepristone.

Modernly, physicians can use mifepristone (Korlym®) to treat patients with Cushing's syndrome. Mifepristone works by a different mechanism than ketoconazole. Rather than lowering cortisol levels, mifepristone reduces the level of cortisol activity by competing for

cortisol at cortisol's primary binding site – GR. As the level of cortisol activity at the GR drops, the symptoms of patients with Cushing's syndrome improve.

In animal models, cardiotoxicity and hepatoxicity were observed with high doses of mifepristone. Following oral intake in humans, mifepristone is extensively metabolized by demethylation and hydroxylation, the initial metabolic steps are catalyzed by the cytochrome P450 (CYP) enzyme CYP3A4. The three most proximal metabolites of mifepristone, namely the monodemethylated, didemethylated and hydroxylated metabolites of mifepristone, all retain considerable affinity toward glucocorticoid receptors. Mifepristone excretion is mainly fecal with less than 10% of the dose recovered in the urine . Based on the available evidence, the FDA did not approve mifepristone in doses higher than 1200 mg/day.

As explained in detail below, patients with Cushing's syndrome are susceptible to fungal, viral, and bacterial infections. They often suffer from depression. Among the drugs used to treat these secondary medical conditions are those that selectively inhibit CYP3A. Until the subject invention was discovered, good medical practice did not recommend combining drugs that inhibit CYP3A with mifepristone. This was because of concern that co-administration would raise mifepristone to toxic levels.

In addition to combining drugs to treat secondary medical disorders associated with Cushing's syndrome, there is motivation to combine ketoconazole with mifepristone to treat the primary condition of Cushing's syndrome – overproduction of cortisol. By antagonizing the GR, mifepristone inhibits the normal feedback loop for cortisol and causes cortisol levels to increase further in many patients. As cortisol levels rise, cortisol binding at MR becomes more frequent and this can result in dangerously low potassium levels – a serious adverse event known as hypokalemia. Hypokalemia is a side effect experienced by approximately 40 percent of the patients taking mifepristone to treat Cushing's syndrome.

Concerned that CYP3A inhibition would lead to dangerously high levels of mifepristone, the FDA limited the recommended dose of mifepristone for patients also receiving strong CYP3A inhibitors such as ketoconazole to 300 mg/day. This is in contrast to the FDA allowing mifepristone doses of up to 1200 mg/day in patients not receiving a strong CYP3A inhibitor. As explained below, doses of mifepristone at or below 300 mg/day give rise to serious questions of therapeutic effectiveness. In the clinical trials presented in the subject application, it was surprisingly determined that mifepristone can be safely combined with CYP3A inhibitors at

doses recognized by the medical community as effective. This discovery has significant advantages to patients.

6. COMBINING CYP3A INHIBITORS AND MIFEPRISTONE

Patients with Cushing's syndrome patients are immune suppressed. They benefit from the co-administration of mifepristone and with drugs that are strong CYP3A inhibitors. For example, doctors may wish to administer antibiotics that are strong CYP3A inhibitors to treat bacterial infections. Examples include clarithromycin and telithromycin. Other strong CYP3A inhibitors such as ketoconazole and itraconazole are commonly prescribed to treat fungal, viral, and yeast infections. The CYP3A inhibitor, cimetidine is prescribed to treat heartburn and ulcers. Notably, the combination of ketoconazole, a drug that inhibits cortisol production and mifepristone, a drug that both blocks cortisol action at the GR and elevates cortisol levels can alleviate a patient's symptoms of Cushing's syndrome via two different mechanisms of action. Ketoconazole reduces levels of cortisol and mifepristone reduce the impact of cortisol on the GR. Normalizing cortisol activity at the GR while preventing cortisol levels from spiking has the advantage of reducing the probability of adverse events stemming from cortisol binding at MR, *ie.* hypokalemia.

Despite the various motivations to combine drugs with mifepristone and prior to the surprising clinical findings that support the subject patent application, physicians would have been unlikely to treat Cushing's syndrome with combinations of drugs having CYP3A inhibition with mifepristone because they assumed (wrongly, as it turns out), that inhibition of CYP3A would cause mifepristone levels to become dangerously high.

The fears of the FDA and persons of skill were understandable. When an inhibitor of the CYP3A enzyme (such as ketoconazole) is combined with a drug selectively metabolized by that enzyme (such as mifepristone), toxic levels of the second drug can quickly develop. It is an unpredictable phenomenon because some drugs are metabolized by only CYP3A and others are metabolized by multiple members of the P450 CYP family. If selectively metabolized by CYP3A, drug levels can increase to between 7 and 20 times the levels that would be observed if in the absence of the CYP3A inhibitor. We can call this dramatic spike in drug levels, the *Greenblatt effect,* named after one of the investigators who has studied the phenomenon with different drugs (Exhibit 2, Greenblatt and Harmatz, 2015).

To ensure that the Greenblatt effect as it relates to combining CYP3A inhibitors and mifepristone did not endanger patients, the FDA instructed doctors to limit mifepristone to doses of no more than 300 mg/day when combined with ketoconazole or other strong CYP3A inhibitors (See Exhibit 3, 2012 Korlym FDA label). The FDA also required Corcept to test for the Greenblatt effect in healthy adults using a combination of mifepristone and ketoconazole. The FDA stated that "only a clinical trial (rather than a nonclinical or observational study) will be sufficient to characterize the effect of co-administration of strong CYP3A inhibitors on increasing mifepristone drug levels and to assess the potential for the known serious risks of severe hypokalemia and adrenal insufficiency." See Exhibit 4, 2012 FDA Approval Letter for NDA 202107 (signed February 17, 2012).

7. SURPRISING ADVANTAGES

Surprisingly, the FDA-mandated clinical study showed that the combination of mifepristone and ketoconazole did not result in dangerously high levels of mifepristone. The Greenblatt effect was not observed. Mifepristone levels increased by only about 25%. The clinical data is presented in the subject patent application.

The failure to observe the Greenblatt effect was surprising, unpredictable and very advantageous to the Cushing's patient population. These results allowed Corcept to devise a method for administering the drugs in combination – with the clinical benefits described above – without risking the toxicity associated with excessive mifepristone levels.

Had the Greenblatt effect occurred (increasing mifepristone levels between 7 and 20 times), physicians could only have prescribed the drugs together by greatly reducing the dose of mifepristone to about 100 mg/day or less – to well below even the FDA's permitted maximum of 300 mg. At such low mifepristone doses, it is extremely unlikely that patients would have experienced any benefit.

7(a). <u>The Greenblatt effect is unpredictable</u>

The impact of ketoconazole on the AUC and Cmax of a co-administered drug varies with the drug being studied. It ranges from inconsequential changes to increases that are so toxic that the FDA does not recommend combining the drugs under any conditions.

The label for Nizarol (ketoconazole) includes a table of drugs that are known to have toxicity issues when combined with ketoconazole. See Exhibit 5.

Table 1: Selected Drugs That Have Been Shown To or Are Predicted To Have Their Plasma Concentrations Altered By NIZORAL®*

Systemic exposure to these drugs is increased significantly by the addition of ketoconazole. Concomitant use with ketoconazole is contraindicated.	
Alprazolam, midazolam, triazolam	HMG-CoA reductase inhibitors (lovastatin, simvastatin)
Cisapride	Nisoldipine
Dofetilide	Pimozide
Eplerenone	Quinidine
Ergot alkaloids (ergotamine, dihydroergotamine)	
Systemic exposure to these drugs is increased by ketoconazole. Careful monitoring, with possible adjustment in dosage, is recommended	
Alfentanil, fentanyl, sufentanil	Indinavir, saquinavir
Amlodipine, felodipine, nicardipine, nifedipine	Methylpredni-solone
Bosentan	Rifabutin
Buspirone	Sildenafil
Busulfan	Sirolimus (co-administration not recommended)
Carbamazepine	Tacrolimus
Cilostazol	Telithromycin
Cyclosporine	Terfenadine
Digoxin	Trimetrexate
Docetaxel, paclitaxel	Verapamil
Oral anti-coagulants	Vinca alkaloids (vincristine, vinblastine, vinorelbine)

In the text below, there is objective evidence of the unpredictability of the Greenblatt effect.

Midazolam, an anti-anxiolytic benzodiazepine demonstrated an 11.5 fold increase. (See Exhibits 2 and 4)

> Co-administration of NIZORAL® Tablets with alprazolam, midazolam, or triazolam has resulted in elevated plasma concentrations of these drugs. This may potentiate and prolong hypnotic and sedative effects, especially with repeated or chronic administration of these agents. Concomitant administration of NIZORAL® Tablets with alprazolam, oral midazolam, and oral triazolam is contraindicated. (See CONTRAINDICATIONS and WARNINGS sections.) Special precaution and patient monitoring are required with concomitant parenteral midazolam, because the sedative effect may be prolonged.

Exhibit 2, Greenblatt and Harmatz (2015) reported that co-administration with ketoconazole increased midazolam plasma levels by over 11 fold. See Figure 1 on page 344:

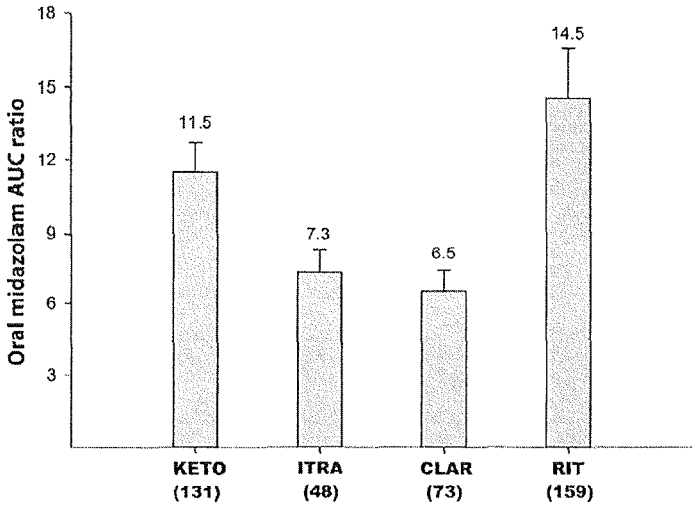


Figure 1

Ratios of total area under the curve (AUC) for oral midazolam during co-administration of each of four inhibitors divided by AUC in the control condition with no inhibitor. Each bar is the mean (±SE) value across studies for the indicated inhibitor, as described in Table 1. KETO ketoconazole, ITRA itraconazole, CLAR clarithromycin, RIT ritonavir. Numbers in parentheses are the total number of subjects participating in studies of the indicated inhibitor

Not all drugs exhibit the Greenblatt effect. See exhibit 6, Kaeser *et al.* (2009) where the antivirals, saquinavir and ritonavir were not excessively elevated when combined with ketoconazole. From page 612 of Kaeser:

TABLE 4. Summary of pharmacokinetic parameters for saquinavir and ritonavir in study arm 1 ($n = 20$)[a]

Parameter	Saquinavir			Ritonavir		
	GM (%CV)		GMR (90% CI)	GM (%CV)		GMR (90% CI)
	Period 1 (− ritonavir)	Period 2 (+ ritonavir + ketoconazole)		Period 1 (− saquinavir)	Period 2 (+ saquinavir + ketoconazole)	
C_{max} (μg/ml)	5.01 (51.5)	5.10 (36.3)	1.02 (0.86–1.20)	1.53 (39.3)	1.66 (26.3)	1.08 (0.96–1.21)
AUC_{0-12} (μg · h/ml)	30.0 (53.3)	32.2 (40.3)	1.07 (0.92–1.26)	8.9 (56.5)	9.95 (30.3)	1.12 (1.03–1.22)
C_{12} (μg/ml)	0.956 (56.3)	1.13 (62.4)	NA	0.230 (57.1)	0.302 (57.7)	NA
T_{max} (h)	3.0 (2.0–6.0)	3.0 (2.0–5.0)	NA	4.0 (2.0–5.0)	4.0 (3.0–5.0)	NA
$t_{1/2}$ (h)	4.9 (4.1–5.9)	5.2 (4.5–6.8)	NA	3.7 (3.1–5.6)	4.2 (3.5–5.5)	NA
$CL_{/F}$ (liter/h)	33.4 (53.3)	25.6 (43.3)	NA	11.2 (56.3)	8.7 (32.8)	NA

[a] GMR, geometric mean ratio of period 2/period 1; GM, geometric mean; NA, not assessed.

Other drugs exhibiting the Greenblatt effect are:

Nisoldipine, a calcium ion blocker with a 24 fold increase (See Exhibit 5)

> Pre-treatment with and concomitant administration of ketoconazole resulted in a 24-fold and 11-fold increase in mean AUC and Cmax of nisoldipine, respectively, compared with treatment with nisoldipine 5 mg alone. **Concomitant administration of ketoconazole with nisoldipine is contraindicated.**

Cisapride, a serotonin 5-HT_4 receptor agonist had an 8 fold increase (See Exhibit 5):

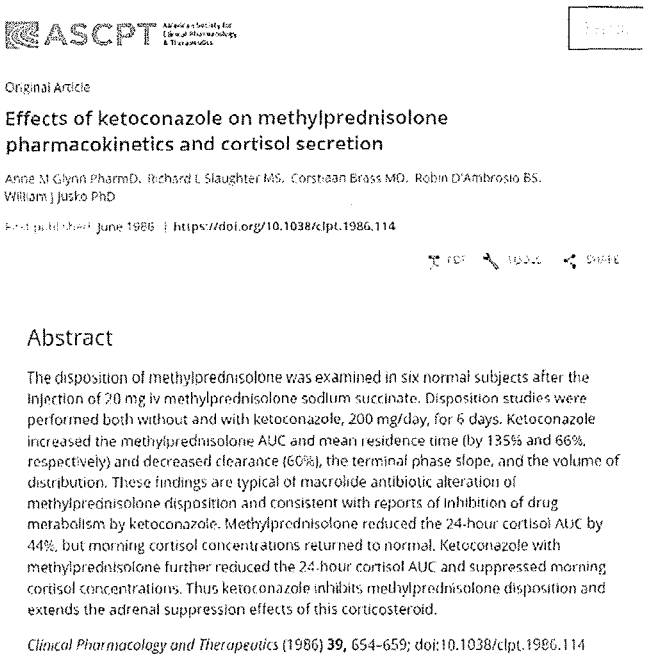
> Oral ketoconazole potently inhibits the metabolism of cisapride resulting in a mean eight-fold increase in AUC of cisapride, which can lead to prolongation of QT interval. Therefore concomitant administration of NIZORAL® Tablets with cisapride is contraindicated

The effect of ketoconazole is *not* predictable as between different steroids.

Eplerenone, a steroidal, antimineralocorticoid is reported to increase by 5 fold (See Exhibit 5)

> Ketoconazole increases the eplerenone AUC by roughly 5-fold, thereby increasing the risk for hyperkalemia. Co-administration of NIZORAL® and eplerenone is contraindicated

Methylprednisolone is increased by 134% See abstract of Glynn et al. 1986:



ASCPT

Original Article

Effects of ketoconazole on methylprednisolone pharmacokinetics and cortisol secretion

Anne M Glynn PharmD, Richard L Slaughter MS, Corshaan Brass MD, Robin D'Ambrosio BS, William J Jusko PhD

First published June 1986 | https://doi.org/10.1038/clpt.1986.114

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Abstract

The disposition of methylprednisolone was examined in six normal subjects after the injection of 20 mg iv methylprednisolone sodium succinate. Disposition studies were performed both without and with ketoconazole, 200 mg/day, for 6 days. Ketoconazole increased the methylprednisolone AUC and mean residence time (by 135% and 66%, respectively) and decreased clearance (60%), the terminal phase slope, and the volume of distribution. These findings are typical of macrolide antibiotic alteration of methylprednisolone disposition and consistent with reports of inhibition of drug metabolism by ketoconazole. Methylprednisolone reduced the 24-hour cortisol AUC by 44%, but morning cortisol concentrations returned to normal. Ketoconazole with methylprednisolone further reduced the 24-hour cortisol AUC and suppressed morning cortisol concentrations. Thus ketoconazole inhibits methylprednisolone disposition and extends the adrenal suppression effects of this corticosteroid.

Clinical Pharmacology and Therapeutics (1986) **39**, 654–659; doi:10.1038/clpt.1986.114

7(b). The therapeutic benefit of mifepristone at low doses is unpredictable and would require additional clinical studies

The discovery that the Greenblatt effect did not occur when mifepristone is combined with ketoconazole allows Cushing's syndrome patients to use mifepristone at proven therapeutic levels when combined with strong CYP3A inhibitors.

Had the Greenblatt effect applied, and mifepristone levels risen by 7-20 times when combined with a strong CYP3A4 inhibitor, physicians could not have adapted by simply reducing the dose of mifepristone proportionally – from 300 mg per day, for example, to 15-40 mg per day. Achieving therapeutically beneficial plasma levels of mifepristone depends on the amount of mifepristone available to bind GR. When it enters the blood stream, mifepristone is strongly bound by α-1-acid glycoprotein (AAG, also known as orosomucoid). High-affinity binding by AAG removes much of the free mifepristone in plasma, rendering it unavailable to bind GR. An appropriate dose of mifepristone must provide enough drug to overcome AAG binding and provide free drug to bind at GR. Because AAG binding absorbs a significant and

unpredictable portion of a 300 mg mifepristone dose, it is unlikely that a lower dose would have any benefit to patients.

In the seminal clinical study, Exhibit 7 - Fleseriu *et al.* (2012) that led to the approval of mifepristone for the treatment of Cushing's syndrome, the authors wrote on page 2042, column 1:

> The most common doses among responders at wk 24/ET were 600 mg (40%) and 1200 mg (40%), followed by 300 mg (13.3%) and 900 mg (6.7%).

In real world clinical practice, the arithmetic average dose of mifepristone to effectively control Cushing's syndrome is just over 800 mg/day.

If the Greenblatt effect had been observed causing mifepristone blood levels to dramatically increase, the FDA's original recommendation of no more than 300 mg/day would have had to be lowered by another 3-fold to 100 mg/day or less. At those low doses, the capacity of a patient's AAG to bind mifepristone would have been controlling of therapeutic effect because at low doses, the mifepristone would have been mostly bound by the AAG and unavailable to antagonize at its target, GR.

In summary, low doses of mifepristone are therapeutically ineffective due to AAG binding. The binding of mifepristone to AAG means that physicians could not have simply reduced the dose of mifepristone and have expected a therapeutic response by patients with Cushing's syndrome. Even at the FDA's originally required maximum dose of 300 mg/day, it is unclear that the therapeutic benefits of mifepristone would be observed in a majority of patients when co-administered with a strong CYP3A inhibitor.

At a minimum, additional clinical studies would have had to be conducted to determine whether low doses of mifepristone in the presence of ketoconazole or other CYP3A inhibitor were clinically effective and safe. Because low levels of mifepristone of $\leq$300 mg/day were known to be ineffective for the majority of patients with Cushing's syndrome, the therapeutic profile of mifepristone in patients would have had to be established for those patients in need of combination therapy. To do otherwise would have been medically unethical. Such studies

would have cost tens of millions of dollars and delayed the availability of mifepristone for this patient group for 3-5 years.

Fortunately and surprisingly, the results presented by Applicants in the subject application demonstrate that mifepristone is not subject to the Greenblatt effect. There is only about a 25% increase in blood levels of mifepristone in the presence of ketoconazole. This means that the claimed methods, requiring a 25% reduction in the original mifepristone dose when administered in the presence of CYP3A inhibitors like ketoconazole, provide safe and therapeutically effective levels of mifepristone. The claimed invention allows for immediate relief for patients with Cushing's syndrome who would benefit from taking both drugs.

The FDA recognized the importance of the study presented in the subject application; based on this new data, in 2017 the FDA revised the 2012 label to allow a dose of mifepristone in the presence of a strong CYP3A inhibitor that is double the originally recommended dose (Exhibit 8).

> • *Use of Strong CYP3A Inhibitors:* Concomitant use can increase mifepristone plasma levels. Use only when necessary and limit mifepristone dose to 600 mg (5.6).

A further increase in the recommended dose is anticipated by Corcept, based on the new research findings described in the instant patent application.

8. The present methods allow for treatment of other conditions while treating Cushing's syndrome

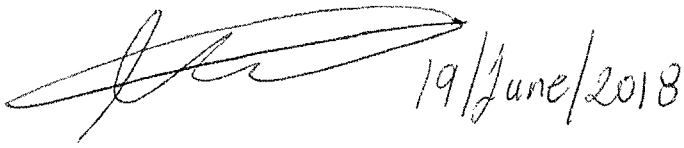
As stated above, patients suffering from Cushing's syndrome often suffer from other diseases or conditions as well. The suppression of the immune system caused by excess cortisol make patients susceptible to infections. For example, fungal infections (for which ketoconazole, itraconazole, voriconazole, and posaconazole are typically prescribed) are common in Cushing's syndrome patients. Cushing's syndrome patients often suffer from ulcers or other gastrointestinal disorders (for which cimetidine, a CYP3A inhibitor, may be prescribed). Doctors may wish to prescribe strong CYP3A inhibiting antibiotics such as clarithromycin and telithromycin to treat bacterial infections. Cushing's syndrome patients often suffer depression, which appears to be

causally related to their high cortisol levels. The antidepressant nefazodone is a strong CYP3A inhibitor. Prior to the applicant's work and per the warnings and precautions in the FDA label, Cushing's syndrome patients requiring more than 300 mg/day mifepristone could not safely be prescribed any of the strong CYP3A inhibitors commonly prescribed to treat secondary conditions often observed in patients with Cushing's syndrome.

The novel methods of the claims, based on the surprising results disclosed in this application, allow for the concomitant use of CYP3A inhibitors with up to 900 mg/day mifepristone. Thus, the methods of the pending claims provide surprising advantages to the patient with Cushing's syndrome, by providing additional treatment options previously unavailable to those patients requiring more than 300 mg mifepristone per day. Finally, the discovery embodied in the subject claims permits patients to safely combine drugs without the years of delay that would have been required had the Greenblatt effect been observed and low dose clinical trials mandated to assure the clinical effectiveness of low doses of mifepristone when combined with CYP3A inhibiting drugs.

The Declarant has nothing further to say.

Dr. Andreas Moraitis



Attachments: Exhibit 1 – Dr. Moraitis' CV
Exhibit 2 – Greenblatt and Harmatz (2015)
Exhibit 3 – 2012 FDA Korlym Label
Exhibit 4 – 2012 FDA Approval Letter
Exhibit 5 – Nizoral Label
Exhibit 6 – Kaeser et al., (2009)
Exhibit 7 – Feseriu *et al.* (2012)
Exhibit 8 – 2017 Revised FDA Korlym Label

EXHIBIT 1 – CV of Dr. Andreas Moraitis

Andreas *G.* Moraitis M.D.
Medical Director
Corcept Therapeutics
149 Commonwealth Drive, Menlo Park, CA 94025
amoraitis@corcept.com

Education and Training

- Medical School: National and Kapodistrian University of Athens 10/1995 to 02/2002
- Military service: Greek Military Air Force 07/2003 to 12/2004
- Internship: Hygeia Athens Hospital (Affiliated with Harvard Medical International) 12/2004 to 10/2006
- Residency: Attikon, Athens University Hospital 10/2006 to 06/2007
- Residency: New York Downtown Hospital/Weill Cornell 07/2007 to 06/2010
- Fellowship: National Institutes of Health Inter-Institutional Program: Adult and Reproductive Endocrinology 06/2010 to 09/2012

Academic, Administrative, and Clinical Appointments

- Clinical Assistant Professor, Endocrine Oncology Program University of Michigan 10/2012 to 6/2014
- Clinical and Research Faculty at the VA Medical Center Orlando Florida 6-2017 to present

Current position

Medical Director, Corcept Therapeutics since 06/2014

Current role and responsibilities:

- Design of phase 1, 2 and 3 clinical trials.
- Working with regulatory for IND submissions
- Medical Monitor in phase 1, 2 and 3 clinical trials.
- Currently I am the medical monitor in two prospective clinical trials and a retrospective study:
    1. An open label, multicenter (US and EU), phase 2 clinical trial with a new selective GR antagonist (CORT125134), in patients with Cushing's syndrome (NCT02804750)

2. Biomarker Expression in Patients With ACTH-Dependent Cushing's Syndrome Before and After Surgery (NCT02922257)

3. Retrospective Chart Review Study of Korlym for the Treatment of ACTH Independent Cushing's Syndrome (NCT02663609).

- Involved in intellectual property generation in oncology and endocrinology diseases.
- PRC and MRC responsibilities

Certification and Licensure

• Metabolism Endocrinology and Diabetes	10/2012
• Internal Medicine Board certified	08/2010
• Maryland Board of Physicians	02/2010
• Virginia Board of Physicians	11/2011
• Michigan Boards of Physicians	10/2012
• Florida Boards of Physicians	06/2015

Research Interests

1. Research and Development of Glucocorticoid Receptor Antagonists

2. Research and Development of markers of glucocorticoid receptor activity(FKBP5).

3. Primary aldosteronism. Genetics of the familial forms of endocrine hypertension, especially familial hyperaldosteronism type2.

4. Genetics of familial forms of pheochromocytoma.

5. Cushing's syndrome: investigation of metabolic and cardiovascular abnormalities associated with autonomous cortisol secretion.

6. Genetics, sub classification, metabolic, bone and cardiovascular complications associated with ACTH independent macro-nodular adrenal hyperplasia.

7. Evaluation of adrenal function in critical illness and cancer. Effect of IL-10 on lipid metabolism and adrenal function.

8. Glucocorticoid receptor antagonists in pancreatic cancer

9. Glucocorticoid receptor antagonists and somatostatin receptors expression- radiologic imaging and clinical implications

10. Glucocorticoid receptor antagonists in secondary adrenal insufficiency

11. Glucocorticoid receptor antagonists in hypertension and osteoporosis

12. Glucocorticoid receptor antagonists in fatty liver disease

13. Glucocorticoid receptor antagonists in the treatment of neuroepithelial tumors

14. Glucocorticoid receptor antagonists in the treatment of PCOS

15. Glucocorticoid receptor antagonists in the treatment of GH excess syndrome

Current Research Activity

1. Retrospective chart review study of Korlym for the treatment of ACTH independent Cushing's syndrome

2. Phase 2 Study of the Safety and Efficacy of CORT125134 in the Treatment of Endogenous Cushing'sSyndrome

3. Evaluation of a novel GR activity marker (FKBP5) for the diagnosis of Cushing's syndrome and as a monitoring tool during medical therapy for CS

Research activity at the National Institutes of Health

Associate extramural investigator in the following protocols at the NIH:

1. Protocol 00-CH-0160: a study involving patients with adrenocortical hypersecretion syndromes and adrenocortical neoplasms. Investigation of the natural history, co morbidities and genetic causes of primary aldosteronism and cortisol secreting adrenal tumors.

2. Protocol 07-CH-0192: a study involving patients with hematopoietic neoplasias who underwent stem cell transplant, primary goal of the study is the investigation and management of endocrinopathies before and after transplantation.

3. Protocol 97-CH-0076: a study involving patients (pediatric and adults) with pituitary abnormalities

Research activity at the University of Michigan

1. A Phase 1, Single-Blind, Placebo-Controlled, Fixed-Sequence, Single-Dose Study to Evaluate the Safety and Tolerability of NBI 77860 in Adult Females with Congenital Adrenal Hyperplasia (NBI77860-1301)

2. A multicenter, international, randomized, parallel group, double-blind, placebo-controlled Cardiovascular Safety & Renal Microvascular outcome study with Linagliptin, 5 mg once daily in patients with type 2 diabetes mellitus at high vascular risk (CARMELINA)

Intellectual Property

- Glucocorticoid receptor antagonists in combination with somatostatin analogues for the treatment of ACTH producing tumors
- Glucocorticoid receptor antagonists for the treatment of secondary adrenal insufficiency
- Glucocorticoid receptor antagonists for the differential diagnosis of Ectopic ACTH Cushing's syndrome from Cushing disease
- Development of a new marker for glucocorticoid receptor activity (FKBP5), as a monitoring tool of cortisol excess
- Glucocorticoid Receptor Antagonists for the treatment of Neuroepithelial tumors
- Glucocorticoid Receptor Antagonists for the treatment of acromegaly.
- Glucocorticoid receptor antagonists for the treatment of catecholamine producing tumors

HONORS AND AWARS

- Multiple awards for top performance in Medical School 10/1998 to2/2002
- NATO award for excellent medical services in Aktion AWACS base: support of the AWACS' crews during the Olympic Games, August2004
- Outstanding rotating senior resident award, Sloan Kettering Memorial Hospital December 2008
- Award for exceptional performance as assistant chief resident in Internal Medicine, June 2010
- Outstanding Senior resident of the year, June 2010
- The John T Flynn young investigator award for outstanding independent scholarly achievement during the Internal medicine residency training, June2010
- Award for outstanding volunteer service to the Endocrine mobile med and the community of the Montgomery county, June2012
- Presidential poster competition award at the 94th annual meeting & expo of the endocrine society, Houston Texas June 23-26, 2012
- Make the difference award: University of Michigan6/2013
- America's Top Physicians- (2014 and 2015)
- Leading Physician of the World 2016(International Association of Healthcare Professionals)

Memberships in Professional Societies

- Member of the Endocrine society
- Member of the American Association of Clinical Endocrinologists
- Member of the American Medical Association
- Member of Florida Medical Association
- Member of European Society of Medical Oncology
- Member of the Pituitary Society
- Member of Pituitary Professional Group

Editorial Positions, Boards and Peer-Review Service

- Reviewer for the European Journal of Endocrinology since August 2011
- Reviewer for the Journal of Clinical Endocrinology and Metabolism since September 2011
- Associate faculty for the F1000 since 11/2012
- Reviewer for the World Journal of Surgery since 6/2013
- Reviewer for the Endocrine Practice Journal since 1/2014
- Reviewer for PLOS since 1/2015

Committee, Organizational and Volunteer Services

• Assistant Chief Resident, New York Downtown Hospital	07/2009 to 06/2010
• Volunteer Endocrinology services for the mobile medclinic and the community of the Montgomerycounty (Maryland)	07/2011 to 07/2012
• Volunteer Clinical Faculty at the VA Medical Center Orlando Florida	06/2017 to present

Bibliography

1. **Evaluation of Evidence of Adrenal Insufficiency in Trials of Normocortisolemic Patients Treated With Mifepristone**
   Kevin Yuen, Andreas Moraitis, Dat Nguyen
   Journal of the endocrine society, 2017

2. **Nonfunctional adrenal adenomas: truth or myth? Presentation and treatment of 2 patients**
   Andreas G. Moraitis
   AACE Clinical Case Reports, 2017

3. **The role of glucocorticoid receptors in metabolic syndrome and psychiatric illness.**
   Andreas G. Moraitis MD, Thaddeus Block MD, Dat Nguyen, Joseph K. Belanoff MD
   The Journal of Steroid Biochemistry and Molecular Biology 2016

4. **Mifepristone Improves Octreotide Efficacy in ResistantEctopicCushing's Syndrome**
   Andreas G. Moraitis, MD and Richard J. Auchus, MD, PhD, FACE
   Case Rep Endocrinol 2016

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9. **Elevated interleukin-10: A new cause of dyslipidemia leadingto severe HDL deficiency**
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Selected Abstracts.

1. **IMPROVED RESPONSE TO OCTREOTIDE LAR FOR ECTOPIC CUSHING'S SYNDROME DURING MIFEPRISTONE THERAPY: A CASE STUDY.**
   Andreas G. Moraitis, MD,* and Richard J. Auchus, MD, PhD,FACE
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2. **HDL disappearance syndrome associated with intravascular lymphoma.**
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3. **Is primary hyperaldosteronism due to unilateral hyperplasia actuallyearly evidence of bilateralhyperplasia?**
   Mitra Rauschecker, Andreas G Moraitis, Constantine Stratakis, Abraham SB
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4. **Aldosterone and cortisol co-secreting adenomas: a retrospective study**
   Andreas G Moraitis, Rauschecker ML, Abraham SB, Constantine A. Stratakis
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5. **Interleukin-10 Decreases HDL: A Novel Cause of Disappearing HDL Syndrome**
   Lita A Freeman; Andreas G Moraitis; Robert Shamburek; Wyndham Wilson; Cliona M Grant; Koneti Rao; Susan Price; Ronald L Hornung; Thomas Fleisher; Frank Pucino; Gabor G Illei; Alan TRemaley
   Arteriosclerosis, Thrombosis and vascular biology

6. **A Modified Saline Suppression Test to Confirm the Diagnosis ofPrimary Aldosteronism**
   Mitra Lynn Rauschecker, MD, Andreas Moraitis, MD, Charalampos Lyssikatos, MD, Elena Belyavskaya, MD, Smita Baid Abraham, MD and Constantine A Stratakis, MD
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7. **Bleeding Adrenal: Adrenal Hemorrhage as a Complication of AdrenalVenous Sampling**
   Jalaja Joseph, Charalampos Lyssikatos, Andreas Moraitis, Mitra Lynn Rauschecker, Smita Baid Abraham and Constantine A Stratakis
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8. **Gigantism: Results of an International Clinical and GeneticStudy**
   Liliya Rostomyan, MD1, Adrian F Daly, MB,BCh,PhD1, Anurag Lila, MD2, Anne-Lise Lecoq, MD3, Emil Nachev, MD4, Andreas Moraitis, MD5, Luciana Ansaneli Naves, MD PhD6, Dianne Kranenburg, MD7, Ian MacMurray Holdaway, FRAC,MBCB,MD8, Silvia Filipponi, MD9, Caroline Jung-Sievers, MD10, Mona Sahnoun-Fathallah, MD11, Marja Ojaniemi, MD PhD12, Ekaterina Sorkina, MD13, Maria Tichomirowa, MD1, Irena Ilovaiskaya, MD PhD14, Margaret Zacharin, MD15, Jerome Yves Bertherat, MDPhD16, Elena Malchiodi, MD17, Roberto Salvatori, MD18, Sandrine Laboureau-Soares

Barbosa, MD19, Dominique M Maiter, MDPhD20, Ann I McCormack, MD21, Klaus Von Werder, MDFRCP22, Jacob Dal, MD23, Elena Nazzari, MD24, Renata Simona Auriemma, MD25, Daniel L Metzger, MD26, Jens Otto Jorgensen, MDPhD23, Tapani Ebeling, MDPhD12, Diego Ferone, MDPhD24, Gunter Karl Stalla, MD10, Paolo Beck-Peccoz, MD17, Lauri Aaltonen, MD PhD27, Annamaria Colao, MD PhD25, Vyacheslav Pronin, MD PhD13, Anne Barlier, MDPhD28, Thierry Brue, MD PhD11, Vincent Rohmer, MD19, Satinath Mukhopadhyay, MDDM29, Francoise Borson-Chazot, MDPhD30, Sebastian JCMM Neggers, MD PhD7, Marie-Lise Jaffrain-Rea, MD PhD31, Constantine A Stratakis, MD D(MDSc32, Philippe Chanson3, Sabina Zacharieva, MD4, Patrick Petrossians, MD1, Nalini Shah, DM2 and Albert Beckers, MDPhD1
Endocr Rev, Vol. 34 (03_MeetingAbstracts): OR20-6

Selected Presentations

1. Endocrine Society meeting, Chicago 2018. Introduction to the Pharmaceutical Industry

2. Endocrine Nurses Society, Twenty-Seventh Annual Symposium Orlando. April 2017: Update on Adrenal Insufficiency and "Adrenal Fatigue"

3. Barrow Pituitary Symposium Focus: Management of Pituitary Tumors 11-5-2016 Phoenix Arizona : Treating Patients with Hypercortisolism: Mild to Overt Cushing's Syndrome

4. Endocrine Grand rounds, University of South California 4-26-2016: Adrenal Cushing's syndrome

5. 11th Annual Contemporary Issues in Pituitary Disease: Cleveland Clinic March 11, 2016: Treating Patients with ACTH Dependent Cushing's syndrome

6. Endocrine Grand Rounds, Yale University 2-12-2016: Adrenal Cushing's syndrome

7. Endocrine Grand Rounds, Emory University 12-8-2015: "Adrenal Cushing's Syndrome"

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on July 18, 2018

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Jo Ann Honcik Dallara/
Jo Ann Honcik Dallara

PATENT
Attorney Docket No.: 085178-1053027-011410US
Client Ref. No.:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Confirmation No.: 2957
Joseph K. Belanoff	Examiner: Chris E. Simmons
Application No.: 15/627,359	Technology Center/Art Unit: 1629
Filed: June 19, 2017	
For: CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A OR STEROIDOGENESIS INHIBITORS	SECOND RULE 132 DECLARATION BY DR. ANDREAS MORAITIS
Customer No.: 144579	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

I, Dr. Andreas Moraitis, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true. The Exhibits (1-8) attached to my earlier Rule 132 Declaration dated June 19, 2018 are incorporated herein by reference.

2. I received a medical doctorate from the National and Kapodistrian University of Athens, Greece, in 2002, and received fellowship training in adult and reproductive

endocrinology at the U.S. National Institutes of Health (2010-2012). I am a board certified in internal medicine by the American Board of Internal Medicine and am board certified in endocrinology by the American Board of Endocrinology and Metabolism. I held the academic appointment of Assistant Professor, Endocrine Oncology, at the University of Michigan Medical School (2012-2014). I am presently employed Corcept Therapeutics, Inc. where I am Director of Clinical Development. I have treated Cushing's syndrome patients and I am familiar with modern medical treatments for patients with Cushing's syndrome. My *curriculum vitae* is attached as Exhibit 1.

3. I have read the subject application USSN 15/627,359, the outstanding final Office Action dated June 12, 2018 and the prior art references cited by the Examiner (Korlym® 2012 Package Insert, WO 2009/050136 Ulmann and Kaeser (2009)). I understand that the Examiner believes the pending claims to be obvious over the Package Insert as a primary reference with Ulmann as a secondary reference.

4. My first declaration dated June 19, 2018, first submitted to the USPTO on June 29, 2018 for USSN 15/627,368, is submitted along with this second declaration to provide evidence of surprising advantages sufficient to traverse the outstanding rejection. This second declaration is intended to provide evidence of how a practicing physician would read and understand the 2012 Package Insert with knowledge of Ulmann and Kaeser. In brief, it appears that the Examiner has interpreted the Package Insert in a manner that contradicts the plain meaning of the language. His reasoning conflates the general instructions for optimizing mifepristone doses in the absence of CYP3A inhibitors with express instructions not to exceed 300 mg/day of mifepristone when combining mifepristone with CYP3A inhibitors. In addition, the Examiner urges that Ulmann is motivation for an artisan to act contrary to the express instructions of the Package Insert. Ulmann teaches that mifepristone can be combined with cortisol synthesis inhibitors including ketoconazole to prevent spikes in cortisol levels attributed to mifepristone. Ulmann does not address the effect of co-administration of ketoconazole on mifepristone levels. Kaeser is addressed in my first Rule 132 Declaration at section 7a, page 8.

5. As I read the outstanding Office Action, the Examiner repeatedly states that an artisan, a doctor treating patients with Korlym, reading the 2012 Package Insert and the 2009 Ulmann patent application would have understood or have been motivated to dose mifepristone in 300 mg increments up to 1200 mg/day when combined with CYP3A inhibitor. This statement is repeated at pages 6 - 8 of the final Office Action:

> One of ordinary skill in the art would have found it obvious to treat hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome with a composition containing mifepristone and ketoconazole. The artisan would have understood that both mifepristone and ketoconazole are taught to be used for treating Cushing's diseases and may be combined for that purpose (Ulmann). When combined, the artisan would have further recognized that a "reduction of mifepristone may be required". Thus, if the Cushing's patient is treated with 1200 mg or 900 mg as disclosed by the package insert and it is found to be beneficial to combine with ketoconazole, then **the artisan would have understood that the concentration of mifepristone may be adjusted by 300 mg increments and as tolerated (see package insert).**
>
> While the prior art does not specifically lower mifepristone dosage to 300 mg and titrating it up to 600 mg, one of ordinary skill in the art would have understood that while lowering it to 300 mg is the more preferred dose of mifepristone when combine with ketoconazole, **the artisan would have recognized that the dose should be adjusted as tolerated while considering the benefits and costs for using the combination of drugs for treatment.**
>
> As outlined above, the package insert teaches that the adjustment of dose of mifepristone based on clinical tolerance and clinical response. Thus, one of ordinary skill in the art would have understood that while lowering it to 300 mg is the more preferred dose of mifepristone when combine with ketoconazole, **the artisan would have recognized that the dose should be adjusted as tolerated while considering the benefits and costs for using the combination of drugs for treatment.**

In the above text, the Examiner has conflated the 2012 Package Insert's general instructions concerning dose titration with the express statements in the Label not to exceed 300 mg/day when mifepristone is combined with a CYP3A inhibitor. In doing so, the Examiner supports his rejection on a misreading of the Package Insert directly contradicting its plain meaning.

6. When combined with CYP3A inhibitors, the label expressly states that the dose of mifepristone should not exceed 300 mg/ml. See page 1 of Exhibit 2 – Package Insert:

> • CYP3A inhibitors: Caution should be used when Korlym is used with strong CYP3A inhibitors. Limit mifepristone dose to 300 mg per day when used with strong CYP3A inhibitors (5.6, 7.2).

The above text is expressly informing physicians not to exceed 300 mg/day of mifepristone when combined with CYP3A inhibitors. This express directive clearly supplants the general directions to up-titrate dosing of mifepristone from 300 to 1200 mg/day to optimize patient. From Page 1 of the Package Insert:

> ----------DOSAGE AND ADMINISTRATION----------
> - Administer once daily orally with a meal (2).
> - The recommended starting dose is 300 mg once daily (2).
> - Renal impairment: do not exceed 600 mg once daily.
> - Mild-to-moderate hepatic impairment: do not exceed 600 mg once daily. Do not use in severe hepatic impairment.
>
> Based on clinical response and tolerability, the dose may be increased in 300 mg increments to a maximum of 1200 mg once daily. Do not exceed 20 mg/kg per day (2).

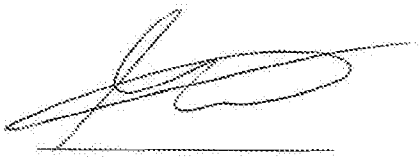
FDA approved Package Inserts are recommendations for good medical practice. Practicing physicians such as myself view Package Insert as important guidelines for treating their patients. While physicians are legally permitted to go *off label*, they do so at their own risk of legal liability. In my experience, this is a rare event and most commonly occurs for alternative, non-approved medical indications. It is one thing to prescribe a drug for an off-label use at generally accepted safe doses. It is quite another to treat a patient with drug doses that are counter to the express warnings of the label. This is especially true when those warnings are presenting clear and obvious concerns over toxicity.

While the Ulmann (2009) reference suggests a reason to combine mifepristone with inhibitors of cortisol synthesis including ketoconazole, the 2012 FDA Package Insert is a legally mandated and FDA approved document. Its primary purpose is patient safety. When the Package Insert is read in combination with the teachings of Ulmann (2009), the combination would not motivate a competent physician of ordinary skill to combine more than 300 mg/day of mifepristone with a CYP3A inhibitor including ketoconazole in an attempt to optimize the benefits of mifepristone.

7. As a clinician who has treated patients with Cushing's disease with mifepristone and for the reasons stated above, I respectfully submit that the Examiner's reasoning for rejecting the

pending claims goes well beyond the plain meaning of the 2012 Package Insert and is not how an artisan of ordinary skill would interpret the text of the Package Insert even with knowledge of Ulmann.

The Declarant has nothing further to say.



16/July/2018

Dr. Andreas Moraitis Date

Referenced Attachments: Exhibit 1 – Dr. Moraitis' CV
Exhibit 3 – 2012 FDA Korlym Label

KILPATRICK TOWNSEND & STOCKTON LLP

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on June 28, 2018

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Jo Ann Honcik Dallara/
Jo Ann Honcik Dallara

PATENT
Attorney Docket No.: 085178-1053029-011420US
Client Ref. No.:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Joseph K. Belanoff Application No.: 15/627,368 Filed: June 19, 2017 For: CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A OR STEROIDOGENESIS INHIBITORS Customer No.: 144579	Confirmation No.: 3411 Examiner: Barbara P. Badio Technology Center/Art Unit: 1628 RULE 132 DECLARATION BY DR. HANFORD K.S. YAU

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

I, Dr. Hanford K.S. Yau, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true. The Exhibits (1-8) attached hereto are incorporated herein by reference.

2. I received a medical doctorate from the New York Medical College in 2005, and received fellowship training in endocrinology, diabetes and metabolism at the University of Florida, Gainsville College of Medicine from 2012-2014. I am a board certified in internal

medicine by the American Board of Internal Medicine and am board certified in endocrinology by the American Board of Endocrinology and Metabolism. I am a fellow of the American College of Endocrinology and I hold faculty positions at both the University of Central Florida and at the University of California San Francisco (Fresno Division) I have a clinical practice where I routinely treat Cushing's syndrome patients. I am familiar with modern medical treatments for patients with Cushing's syndrome. My *curriculum vitae* is attached as Exhibit 1.

3. I serve as a paid consultant to Corcept Therapeutics, Inc. and I am familiar with the medical use of mifepristone for treating patients with Cushing's syndrome based on my clinical experience. I have read the subject application USSN 15/627,368, the outstanding non-final Office Action dated March 16, 2018 and the prior art reference cited by the Examiner (WO 2009/050136 (Ulmann). I understand that the Examiner believes the pending claims to be obvious over Ulmann.

The purpose of this declaration is to provide objective evidence of surprising advantages sufficient to traverse the outstanding rejection.

4. THE INVENTION

The pending claims recite a dosing regimen for treating Cushing's syndrome with a combination of mifepristone and a CYP3A inhibitor. The specifics of the claimed invention require that original amount of mifepristone in the absence of the CYP3A inhibitor be reduced by at least 25% to a dose that is greater than **800** mg/day when combined with the CYP3A inhibitor. This claim stands in contrast to the FDA original maximum dose of no greater than **300** mg/day when combined with ketoconazole, which is a strong CYP3A inhibitor that is often used to treat patients with Cushing's syndrome. Pending claim 1 reads:

> 1. A method of treating Cushing's syndrome in a patient who is taking a once daily (OD) dose of mifepristone comprising reducing the once-daily dose amount of said mifepristone administered to said patient from an original OD mifepristone dose amount to an adjusted OD mifepristone dose amount that is greater than 800 mg and is at least 25% less than said original OD mifepristone dose amount when the patient is receiving concomitant administration of a CYP3A inhibitor selected from ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole, cobicistat, danoprevir, elvitegravir indinavir, paritaprevir ombitasvir dasabuvir and troleandomycin.

The outstanding obviousness rejection is over Ulmann (WO 2009/0501136). Ulmann teaches the combination of glucocorticoid receptor antagonists (*eg.* mifepristone) and cortisol synthesis inhibitors (*eg.* ketoconazole) to treat patients with Cushing's syndrome. The Examiner finds the claimed invention to be *prima facie* obvious.

As discussed below, based on my clinical training and experience, I find the claimed invention to be unexpected and to provide advantages to patients with Cushing's syndrome and doctors treating them.

5. BACKGROUND

Cushing's syndrome is defined by the overproduction of cortisol. It is a life-threatening disorder typically caused by a tumor. The tumor either produces cortisol or adrenocorticotropic hormone (ACTH). ACTH causes the adrenal glands to produce cortisol. By binding to the glucocorticoid receptor (GR), cortisol performs many essential physiological functions. Cortisol also binds to the mineralocorticoid receptor (MR). Significant cortisol binding at MR occurs when cortisol levels are very high.

The abnormally high levels of cortisol in patients with Cushing's syndrome result in excessive activity at the GR, which causes the symptoms of Cushing's syndrome. These symptoms include hyperglycemia, hypertension, persistent infections, hypokalemia, bone loss, hirsutism, psychosis, depression, hirsutism and other adverse effects. The median life expectancy of untreated patients with severe Cushing's syndrome is approximately five years.

Treating patients with Cushing's syndrome presents complex clinical challenges. Surgery to remove the tumor that is secreting excess cortisol or ACTH is the preferred treatment, but is successful in only 50 percent of patients. In the remaining 50 percent of patients, physicians use drugs to reduce cortisol activity.

Before the FDA's approval of mifepristone to treat Cushing's syndrome in 2012, the standard of care was to administer cortisol synthesis inhibitors such as ketoconazole. An undesired side effect of ketoconazole is to strongly inhibit CYP3A. CYP3A is a family of enzymes responsible for the metabolism (i.e., breakdown and clearance) of mifepristone.

Modernly, physicians can use mifepristone (Korlym®) to treat patients with Cushing's syndrome. Mifepristone works by a different mechanism than ketoconazole. Rather than lowering cortisol levels, mifepristone reduces the level of cortisol activity by competing for cortisol at cortisol's primary binding site – GR. As the level of cortisol activity at the GR drops, the symptoms of patients with Cushing's syndrome improve.

In animal models, cardiotoxicity and hepatoxicity were observed with high doses of mifepristone. Following oral intake in humans, mifepristone is extensively metabolized by demethylation and hydroxylation, the initial metabolic steps are catalyzed by the cytochrome P450 (CYP) enzyme CYP3A4. The three most proximal metabolites of mifepristone, namely the monodemethylated, didemethylated and hydroxylated metabolites of mifepristone, all retain considerable affinity toward glucocorticoid receptors. Mifepristone excretion is mainly fecal with less than 10% of the dose recovered in the urine . Based on the available evidence, the FDA did not approve mifepristone in doses higher than 1200 mg/day.

As explained in detail below, patients with Cushing's syndrome are susceptible to fungal, viral, and bacterial infections. They often suffer from depression. Among the drugs used to treat these secondary medical conditions are those that selectively inhibit CYP3A. Until the subject invention was discovered, good medical practice did not recommend combining drugs that inhibit CYP3A with mifepristone. This was because of concern that co-administration would raise mifepristone to toxic levels.

In addition to combining drugs to treat secondary medical disorders associated with Cushing's syndrome, there is motivation to combine ketoconazole with mifepristone to treat the primary condition of Cushing's syndrome – overproduction of cortisol. By antagonizing the GR, mifepristone inhibits the normal feedback loop for cortisol and causes cortisol levels to increase further in many patients. As cortisol levels rise, cortisol binding at MR becomes more frequent and this can result in dangerously low potassium levels – a serious adverse event known as hypokalemia. Hypokalemia is a side effect experienced by approximately 40 percent of the patients taking mifepristone to treat Cushing's syndrome.

Concerned that CYP3A inhibition would lead to dangerously high levels of mifepristone, the FDA limited the recommended dose of mifepristone for patients also receiving strong CYP3A inhibitors such as ketoconazole to 300 mg/day. This is in contrast to the FDA allowing mifepristone doses of up to 1200 mg/day in patients not receiving a strong CYP3A inhibitor. As

explained below, doses of mifepristone at or below 300 mg/day give rise to serious questions of therapeutic effectiveness. In the clinical trials presented in the subject application, it was surprisingly determined that mifepristone can be safely combined with CYP3A inhibitors at doses recognized by the medical community as effective. This discovery has significant advantages to patients.

6. COMBINING CYP3A INHIBITORS AND MIFEPRISTONE

Patients with Cushing's syndrome patients are immune suppressed. They benefit from the co-administration of mifepristone and with drugs that are strong CYP3A inhibitors. For example, doctors may wish to administer antibiotics that are strong CYP3A inhibitors to treat bacterial infections. Examples include clarithromycin and telithromycin. Other strong CYP3A inhibitors such as ketoconazole and intraconazole are commonly prescribed to treat fungal, viral, and yeast infections. The CYP3A inhibitor, cimetidine is prescribed to treat heartburn and ulcers.

Despite various motivations to combine drugs with mifepristone and prior to the surprising clinical findings that support the subject patent application, physicians would have been unlikely to treat Cushing's syndrome with combinations of drugs having CYP3A inhibition with mifepristone because they assumed (wrongly, as it turns out), that inhibition of CYP3A would cause mifepristone levels to become dangerously high.

The fears of the FDA and persons of skill were understandable. When an inhibitor of the CYP3A enzyme (such as ketoconazole) is combined with a drug selectively metabolized by that enzyme (such as mifepristone), toxic levels of the second drug can quickly develop. It is an unpredictable phenomenon because some drugs are metabolized by only CYP3A and others are metabolized by multiple members of the P450 CYP family. If selectively metabolized by CYP3A, drug levels can increase to between 7 and 20 times the levels that would be observed if in the absence of the CYP3A inhibitor. We can call this dramatic spike in drug levels, the *Greenblatt effect,* named after one of the investigators who has studied the phenomenon with different drugs (Exhibit 2, Greenblatt and Harmatz, 2015).

To ensure that the Greenblatt effect as it relates to combining CYP3A inhibitors and mifepristone did not endanger patients, the FDA instructed doctors to limit mifepristone to doses of no more than 300 mg/day when combined with ketoconazole or other strong CYP3A

inhibitors (See Exhibit 3, 2012 Korlym FDA label). The FDA also required Corcept to test for the Greenblatt effect in healthy adults using a combination of mifepristone and ketoconazole. The FDA stated that "only a clinical trial (rather than a nonclinical or observational study) will be sufficient to characterize the effect of co-administration of strong CYP3A inhibitors on increasing mifepristone drug levels and to assess the potential for the known serious risks of severe hypokalemia and adrenal insufficiency." See Exhibit 4, 2012 FDA Approval Letter for NDA 202107 (signed February 17, 2012).

7. SURPRISING ADVANTAGES

Surprisingly, the FDA-mandated clinical study showed that the combination of mifepristone and ketoconazole did not result in dangerously high levels of mifepristone. The Greenblatt effect was not observed. Mifepristone levels increased by only about 25%. The clinical data is presented in the subject patent application.

The failure to observe the Greenblatt effect was surprising, unpredictable and very advantageous to the Cushing's patient population. These results allowed Corcept to devise a method for administering the drugs in combination – with the clinical benefits described above – without risking the toxicity associated with excessive mifepristone levels.

Had the Greenblatt effect occurred (increasing mifepristone levels between 7 and 20 times), physicians could only have prescribed the drugs together by greatly reducing the dose of mifepristone to about 100 mg/day or less – to well below even the FDA's permitted maximum of 300 mg. At such low mifepristone doses, it is extremely unlikely that patients would have experienced any benefit.

7(a). The Greenblatt effect is unpredictable

The impact of ketoconazole on the AUC and Cmax of a co-administered drug varies with the drug being studied. It ranges from inconsequential changes to increases that are so toxic that the FDA does not recommend combining the drugs under any conditions.

The label for Nizarol (ketoconazole) includes a table of drugs that are known to have toxicity issues when combined with ketoconazole. See Exhibit 5.

Table 1: Selected Drugs That Have Been Shown To or Are Predicted To Have Their Plasma Concentrations Altered By NIZORAL®*

Systemic exposure to these drugs is increased significantly by the addition of ketoconazole. Concomitant use with ketoconazole is contraindicated.	
Alprazolam, midazolam, triazolam	HMG-CoA reductase inhibitors (lovastatin, simvastatin)
Cisapride	Nisoldipine
Dofetilide	Pimozide
Eplerenone	Quinidine
Ergot alkaloids (ergotamine, dihydroergotamine)	
Systemic exposure to these drugs is increased by ketoconazole. Careful monitoring, with possible adjustment in dosage, is recommended.	
Alfentanil, fentanyl, sufentanil	Indinavir, saquinavir
Amlodipine, felodipine, nicardipine, nifedipine	Methylprednisolone
Bosentan	Rifabutin
Buspirone	Sildenafil
Busulfan	Sirolimus (co-administration not recommended)
Carbamazepine	Tacrolimus
Cilostazol	Telithromycin
Cyclosporine	Tolterodine
Digoxin	Trimetrexate
Docetaxel, paclitaxel	Verapamil
Oral anti-coagulants	Vinca alkaloids (vinchristine, - vinblastine, vinorelbine)

In the text below, there is objective evidence of the unpredictability of the Greenblatt effect.

Midazolam, an anti-anxiolytic benzodiazepine demonstrated an 11.5 fold increase. (See Exhibits 2 and 4)

> Co-administration of NIZORAL® Tablets with alprazolam, midazolam, or triazolam has resulted in elevated plasma concentrations of these drugs. This may potentiate and prolong hypnotic and sedative effects, especially with repeated or chronic administration of these agents. Concomitant administration of NIZORAL® Tablets with alprazolam, oral midazolam, and oral triazolam is contraindicated. (See CONTRAINDICATIONS and WARNINGS sections.) Special precaution and patient monitoring are required with concomitant parenteral midazolam, because the sedative effect may be prolonged.

Exhibit 2, Greenblatt and Harmatz (2015) reported that co-administration with ketoconazole increased midazolam plasma levels by over 11 fold. See Figure 1 on page 344:

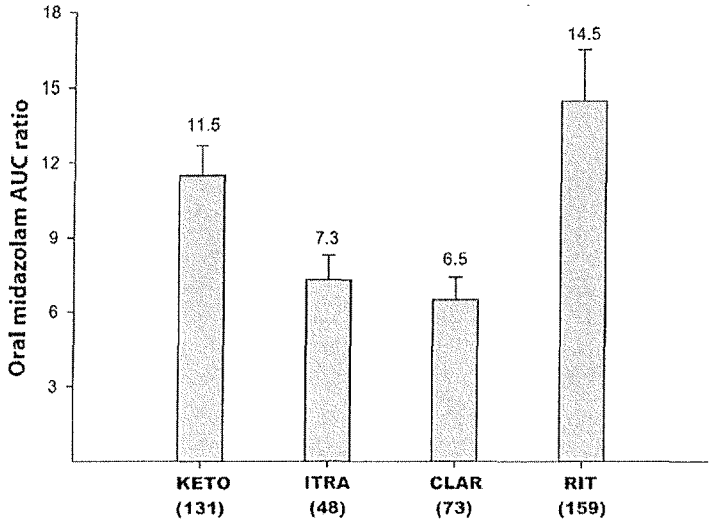


Figure 1

Ratios of total area under the curve (AUC) for oral midazolam during co-administration of each of four inhibitors divided by AUC in the control condition with no inhibitor. Each bar is the mean (±SE) value across studies for the indicated inhibitor, as described in Table 1. KETO ketoconazole, ITRA itraconazole, CLAR clarithromycin, RIT ritonavir. Numbers in parentheses are the total number of subjects participating in studies of the indicated inhibitor

Not all drugs exhibit the Greenblatt effect. See exhibit 6, Kaeser *et al.* (2009) where the antivirals, saquinavir and ritonavir were not excessively elevated when combined with ketoconazole. From page 612 of Kaeser:

TABLE 4. Summary of pharmacokinetic parameters for saquinavir and ritonavir in study arm 1 (n = 20)[a]

Parameter	Saquinavir			Ritonavir		
	GM (%CV)			GM (%CV)		
	Period 1 (+ ritonavir)	Period 2 (+ ritonavir + ketoconazole)	GMR (90% CI)	Period 1 (+ saquinavir)	Period 2 (+ saquinavir + ketoconazole)	GMR (90% CI)
C_{max} (μg/ml)	5.01 (51.5)	5.10 (36.3)	1.02 (0.86–1.20)	1.53 (39.4)	1.66 (26.4)	1.08 (0.96–1.21)
AUC_{0-12} (μg · h/ml)	30.0 (53.5)	32.2 (41.3)	1.07 (0.92–1.26)	8.9 (36.3)	9.93 (30.3)	1.12 (1.03–1.22)
C_{12} (μg/ml)	0.956 (56.3)	1.13 (62.4)	NA	0.230 (57.1)	0.292 (52.7)	NA
T_{max} (h)	3.0 (2.0–6.0)	3.0 (2.0–5.0)	NA	4.0 (2.0–5.0)	4.0 (1.0–5.0)	NA
$t_{1/2}$ (h)	4.9 (3.1–5.9)	5.2 (4.5–6.8)	NA	3.7 (3.1–5.6)	4.2 (3.5–5.5)	NA
CL_{cr}/F (liter/h)	33.4 (53.5)	25.6 (45.3)	NA	11.2 (76.3)	8.7 (32.8)	NA

[a] GMR, geometric mean ratio of period 2/period 1; GM, geometric mean; NA, not assessed

Other drugs exhibiting the Greenblatt effect are:

Nisoldipine, a calcium ion blocker with a 24 fold increase (See Exhibit 5)

> Pre-treatment with and concomitant administration of ketoconazole resulted in a 24-fold and 11-fold increase in mean AUC and Cmax of nisoldipine, respectively, compared with treatment with nisoldipine 5 mg alone. **Concomitant administration of ketoconazole with nisoldipine is contraindicated**.

Cisapride, a serotonin 5-HT receptor agonist had an 8 fold increase (See Exhibit 5):

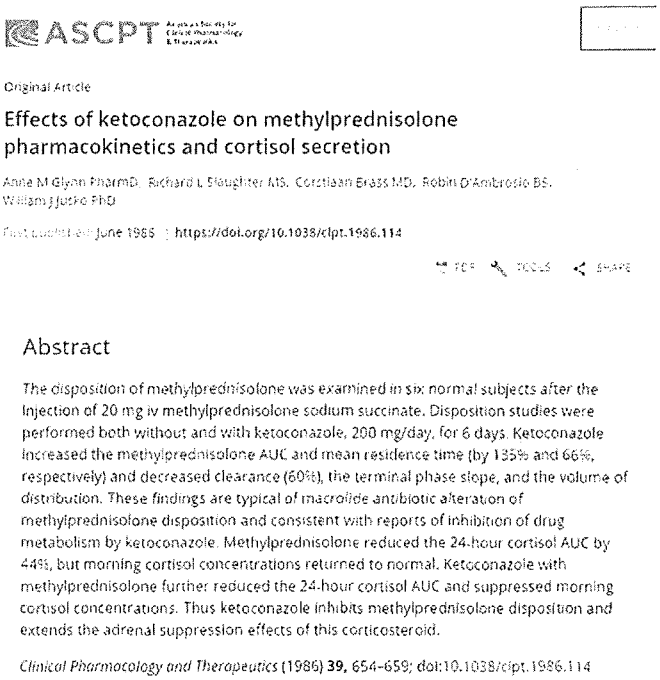
> Oral ketoconazole potently inhibits the metabolism of cisapride resulting in a mean eight-fold increase in AUC of cisapride, which can lead to prolongation of QT interval. Therefore concomitant administration of NIZORAL® Tablets with cisapride is contraindicated

The effect of ketoconazole is *not* predictable as between different steroids.

Eplerenone, a steroidal, antimineralocorticoid is reported to increase by 5 fold (See Exhibit 5)

> Ketoconazole increases the eplerenone AUC by roughly 5-fold, thereby increasing the risk for hyperkalemia. Co-administration of NIZORAL® and eplerenone is contraindicated

Methylprednisolone is increased by 134% See abstract of Glynn et al. 1986:



ASCPT

Original Article

Effects of ketoconazole on methylprednisolone pharmacokinetics and cortisol secretion

Anne M Glynn PharmD, Richard L Slaughter MS, Cordiaan Bras MD, Robin D'Ambrosio BS, William J Jusko PhD

June 1986 | https://doi.org/10.1038/clpt.1986.114

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Abstract

The disposition of methylprednisolone was examined in six normal subjects after the injection of 20 mg iv methylprednisolone sodium succinate. Disposition studies were performed both without and with ketoconazole, 200 mg/day, for 6 days. Ketoconazole increased the methylprednisolone AUC and mean residence time (by 135% and 66%, respectively) and decreased clearance (60%), the terminal phase slope, and the volume of distribution. These findings are typical of macrolide antibiotic alteration of methylprednisolone disposition and consistent with reports of inhibition of drug metabolism by ketoconazole. Methylprednisolone reduced the 24-hour cortisol AUC by 44%, but morning cortisol concentrations returned to normal. Ketoconazole with methylprednisolone further reduced the 24-hour cortisol AUC and suppressed morning cortisol concentrations. Thus ketoconazole inhibits methylprednisolone disposition and extends the adrenal suppression effects of this corticosteroid.

Clinical Pharmacology and Therapeutics (1986) **39**, 654–659; doi:10.1038/clpt.1986.114

7(b). The therapeutic benefit of mifepristone at low doses is unpredictable and would require additional clinical studies

The discovery that the Greenblatt effect did not occur when mifepristone is combined with ketoconazole allows Cushing's syndrome patients to use mifepristone at proven therapeutic levels when combined with strong CYP3A inhibitors.

Had the Greenblatt effect applied, and mifepristone levels risen by 7-20 times when combined with a strong CYP3A4 inhibitor, physicians could not have adapted by simply reducing the dose of mifepristone proportionally – from 300 mg per day, for example, to 15-40 mg per day. Achieving therapeutically beneficial plasma levels of mifepristone depends on the amount of mifepristone available to bind GR. When it enters the blood stream, mifepristone is strongly bound by α-1-acid glycoprotein (AAG, also known as orosomucoid). High-affinity binding by AAG removes much of the free mifepristone in plasma, rendering it unavailable to bind GR. An appropriate dose of mifepristone must provide enough drug to overcome AAG binding and provide free drug to bind at GR. Because AAG binding absorbs a significant and

unpredictable portion of a 300 mg mifepristone dose, it is unlikely that a lower dose would have any benefit to patients.

In the seminal clinical study, Exhibit 7 - Fleseriu *et al.* (2012) that led to the approval of mifepristone for the treatment of Cushing's syndrome. The authors wrote on page 2042, column 1:

> The most common doses among responders at wk 24/ET were 600 mg (40%) and 1200 mg (40%), followed by 300 mg (13.3%) and 900 mg (6.7%).

In real world clinical practice, the arithmetic average dose of mifepristone to effectively control Cushing's syndrome is just over 800 mg/day.

If the Greenblatt effect had been observed causing mifepristone blood levels to dramatically increase, the FDA's original recommendation of no more than 300 mg/day would have had to be lowered by another 3-fold to 100 mg/day or less. At those low doses, the capacity of a patient's AAG to bind mifepristone would have been controlling of therapeutic effect because at low doses, the mifepristone would have been mostly bound by the AAG and unavailable to antagonize at its target, GR.

In summary, low doses of mifepristone are therapeutically ineffective due to AAG binding. The binding of mifepristone to AAG means that physicians could not have simply reduced the dose of mifepristone and have expected a therapeutic response by patients with Cushing's syndrome. Even at the FDA's originally required maximum dose of 300 mg/day, it is unclear that the therapeutic benefits of mifepristone would be observed in a majority of patients when co-administered with a strong CYP3A inhibitor.

At a minimum, additional clinical studies would have had to be conducted to determine whether low doses of mifepristone in the presence of ketoconazole or other CYP3A inhibitor were clinically effective and safe. Because low levels of mifepristone of $\leq$300 mg/day were known to be ineffective for the majority of patients with Cushing's syndrome, the therapeutic profile of mifepristone in patients would have had to be established for those patients in need of combination therapy. To do otherwise would have been medically unethical. Such studies

would have cost tens of millions of dollars and delayed the availability of mifepristone for this patient group for 3-5 years.

Fortunately and surprisingly, the results presented by Applicants in the subject application demonstrate that mifepristone is not subject to the Greenblatt effect. There is only about a 25% increase in blood levels of mifepristone in the presence of ketoconazole. This means that the claimed methods, requiring a 25% reduction in the original mifepristone dose when administered in the presence of CYP3A inhibitors like ketoconazole, provide safe and therapeutically effective levels of mifepristone. The claimed invention allows for immediate relief for patients with Cushing's syndrome who would benefit from taking both drugs.

The FDA recognized the importance of the study presented in the subject application; based on this new data, in 2017 the FDA revised the 2012 label to allow a dose of mifepristone in the presence of a strong CYP3A inhibitor that is double the originally recommended dose (Exhibit 8).

> • *Use of Strong CYP3A Inhibitors:* Concomitant use can increase mifepristone plasma levels. Use only when necessary and limit mifepristone dose to 600 mg (5.6).

A further increase in the recommended dose is anticipated by Corcept, based on the new research findings described in the instant patent application.

8. The present methods allow for treatment of other conditions while treating Cushing's syndrome

As stated above, patients suffering from Cushing's syndrome often suffer from other diseases or conditions as well. The suppression of the immune system caused by excess cortisol make patients susceptible to infections. For example, fungal infections (for which ketoconazole, itraconazole, voriconazole, and posaconazole are typically prescribed) are common in Cushing's syndrome patients. Cushing's syndrome patients often suffer from ulcers or other gastrointestinal disorders (for which cimetidine, a CYP3A inhibitor, may be prescribed). Doctors may wish to prescribe strong CYP3A inhibiting antibiotics such as clarithromycin and telithromycin to treat bacterial infections. Cushing's syndrome patients often suffer depression, which appears to be

causally related to their high cortisol levels. The antidepressant nefazodone is a strong CYP3A inhibitor. Prior to the applicant's work and per the warnings and precautions in the FDA label, Cushing's syndrome patients requiring more than 300 mg/day mifepristone could not safely be prescribed any of the strong CYP3A inhibitors commonly prescribed to treat secondary conditions often observed in patients with Cushing's syndrome.

The novel methods of the claims, based on the surprising results disclosed in this application, allow for the concomitant use of CYP3A inhibitors with up to 900 mg/day mifepristone. Thus, the methods of the pending claims provide surprising advantages to the patient with Cushing's syndrome, by providing additional treatment options previously unavailable to those patients requiring more than 300 mg mifepristone per day. Finally, the discovery embodied in the subject claims permits patients to safely combine drugs without the years of delay that would have been required had the Greenblatt effect been observed and low dose clinical trials mandated to assure the clinical effectiveness of low doses of mifepristone when combined with CYP3A inhibiting drugs.

The Declarant has nothing further to say.

Hanford K.S. Yau

Dr. Hanford K.S. Yau

Attachments: Exhibit 1 – Dr. Moraitis' CV
Exhibit 2 – Greenblatt and Harmatz (2015)
Exhibit 3 – 2012 FDA Korlym Label
Exhibit 4 – 2012 FDA Approval Letter
Exhibit 5 – Nizoral Label
Exhibit 6 – Kaeser et al., (2009)
Exhibit 7 – Feseriu *et al.* (2012)
Exhibit 8 – 2017 Revised FDA Korlym Label

KILPATRICK TOWNSEND & STOCKTON LLP

EXHIBIT 1 – CV of Dr. Hanford K.S. Yau

Hanford K.S. Yau, MD, CCD, FACP, FACE

Personal Information

Professional addresses: 13800 Veterans Way, Clinic 1D, Orlando, FL, 32827
2335 East Kashian Lane, Suite 280, Fresno, CA 93701
Contact: hanfordyau@gmail.com, 914-329-8494
ORCID: http://orcid.org/0000-0003-3143-2407

Education

Undergraduate: The University of California, San Diego, La Jolla, CA
Bachelor of Science in Bioengineering, July 1996 – June 2000
Medical School: New York Medical College, Valhalla, NY
Doctor of Medicine, June 2001 – May 2005
Internship: Naval Medical Center Portsmouth, Portsmouth, VA
Categorical Internal Medicine, June 2005 – July 2006
Residency: Naval Medical Center San Diego, San Diego, CA
Categorical Internal Medicine, July 2008 – June 2010
Fellowship: The University of Florida, Gainesville, FL
Endocrinology, Diabetes, & Metabolism, July 2012 – June 2014

Board Certification

- Board Certified in Endocrinology, Diabetes, & Metabolism, American Board of Internal Medicine, November 2014 – December 2024
- Board Certified in Internal Medicine, American Board of Internal Medicine, August 2010 – December 2020
- Certified Clinical Densitometrist (CCD), International Society of Clinical Densitometry, May 2014 – May 2019

Medical Licensure

California: A96501, original issuance 2006
Florida: ME112651, original issuance 2012
Indiana: 01066483A, original issuance 2009

Honors and Awards

- Fellow of the American College of Physicians (November 2017)
- Fellow of the American College of Endocrinology (November 2017)
- Diplomate of the American Board of Internal Medicine (March 2015)
- American Association of Clinical Endocrinologists 22nd Annual Scientific & Clinical Congress Poster Presentation Awards, Third Place (May 2013)
- Summer Research Fellowship by the New York Medical College Center for Primary Care Education and Research (July 2002)
- The Armed Forces Health Professional Scholarship by the Department of the U.S. Navy (April 2001)
- Certificate of Excellence for Outstanding Research from the Department of Bioengineering, University of California, San Diego (2000)

- Certificate of Recognition for Outstanding Research from the Department of Bioengineering, University of California, San Diego (2000)
- Senior Honors for Academic Excellence from the University of California, San Diego (2000)
- Exemplary Teaching Assistant Award from the Department of Chemistry and Biochemistry, University of California, San Diego (2000)
- Provost Honors (7 awards) for Academic Excellence from the University of California, San Diego (1996 – 2000)
- Lifeline Foundation Student Research Fellowship on Vascular Disease, Manchester, MA (1998)
- Golden Key International Honor Society (induction 1997)

Military Service

United States Navy, Lieutenant Commander, Medical Corp, May 2005 – July 2012, Honorably Discharged

- Navy & Marine Corps Achievement Medal (2 awards)
- National Defense Service Medal
- Armed Forces Expeditionary Medal
- Global War on Terrorism Expeditionary Medal
- Global War on Terrorism Service Medal
- Military Outstanding Volunteer Service Medal
- Navy & Marine Corps Public Health Center Health Promotion & Wellness Award

Professional Positions and Appointments

Staff Endocrinologist, Orlando Veterans Affairs Medical Center, Orlando, FL, September 2015 – Present

- Serving as staff consulting endocrinologist
- Site director of fellowship training in Endocrinology, Diabetes, and Metabolism

Assistant Professor of Internal Medicine, The University of Central Florida, Orlando, FL, April 2016 – Present

- Serving as assistant clinical professor in medicine and endocrinology

Assistant Clinical Professor in Health Sciences, The University of California San Francisco (Fresno Division), Fresno, CA, August 2014 – Present

- Serving as assistant clinical professor in medicine and endocrinology
- Consulting endocrinologist at Community Regional Medical Center, Fresno, CA

Staff Physician, North Florida South Georgia Veterans Health System, Gainesville, FL
Fee Basis Consultant, Department of Internal Medicine, January 2013 – July 2014

Department Head/Staff Physician, Naval Hospital Oak Harbor, WA
Department of Internal Medicine, July 2010 – June 2012

- Appointed as department head from August 2010 – June 2012
- Championed hospital diabetes program and advanced the hospital HEDIS index for cardiovascular, diabetes, and mental health indicators to overall second place in all of Navy Medicine

- Served as the convening authority for medical boards and disability evaluation

Staff Physician, USS BATAAN (LHD 5), Norfolk, VA
Junior Staff Physician, August 2006 – June 2008

- Deployed as primary care physician for 1,500 Naval personnel in support of Operation Iraqi Freedom and Operation Enduring Freedom
- Served as first assistant surgeon to staff general surgeon of Fleet Surgical Team 5
- Provided backup medical logistics and support to the 26th Marine Expeditionary Unit
- Participated in medical civic assistance program in Djibouti, Africa

Institutional, Departmental, and Divisional Administrative Responsibilities

- Appointed and serving as member of ethics consultative committee at Orlando Veterans Affairs Medical Center (May 2016 – Present)
- Appointed and serving as alternate member of the institutional review board (IRB) at Orlando Veterans Medical Center (December 2015 – February 2018)
- Appointed and served as advisor and committee member for pharmacy & therapeutics committee at Community Regional Medical Center (December 2014 – July 2015)
- Appointed and served as advisor for education and evaluation committee at UCSF–Fresno and Community Regional Medical Center (December 2014 – July 2015)
- Appointed and served as subspecialty fellow advisor for housestaff quality and patient safety committee at UF Health System (January 2013 – July 2014)
- Served as subspecialty assistant for diabetes taskforce and inpatient glycemic control work team at UF Health System (September 2013 – July 2014)
- Appointed and served as the public health emergency officer at Naval Hospital Oak Harbor, WA (2011 – 2012)
- Appointed and served as the chairman of the pharmacy & therapeutics committee at Naval Hospital Oak Harbor, WA (2011 – 2012)
- Appointed and served as the chief clinical laboratory officer at Naval Hospital Oak Harbor, WA (2011 – 2012)
- Appointed and served as the physician advisor to the allergy and immunization clinic at Naval Hospital Oak Harbor, WA (2010 – 2012)
- Appointed and served as the resident representative to the Navy Chapter of the American College Physician's Volunteerism Committee (2008 – 2010)

Professional Memberships

- American Thyroid Association, 2012 – Present
- The Endocrine Society, 2012 – Present
- The International Society for Clinical Densitometry, 2011 – Present
  - Serving as clinical osteoporosis joint symposium abstract & clinical case reviewer (2016 – 2017)
  - Serving as a member of the Online CME/Education Committee (2016 – Present)
  - Served as a member of the Certified Clinical Densitometrist Item Writing and Standard Setting Committee (2015 – Present)
- American Association of Clinical Endocrinologists, 2008 – Present
- Council for the Advancement of Diabetes Research and Education, 2006 – Present
- American College of Physician, 2005 – Present

Presentations at National Meetings

American Association of Clinical Endocrinologists 27th Annual Scientific and Clinical Congress, Boston, MA, May 17th, 2018

- Clinical Consequences and Treatment of Hypercortisolism

Piper Jaffray & Co. Biotechnology Equity Research, New York, NY, September 7th, 2017

- Perspective on Hypercortisolism and Development of Medical Therapies

Stifel Financial Corp. Biotechnology Equity Research, Boston, MA, August 17th, 2017

- Perspective on Cushing's Syndrome Treatments

The Florida Endocrine Society, Inc. & AACE – Florida State Chapter, Inc. "Best of the Best: 2017", Orlando, FL, August 5th, 2017

- Clinical Consequences of Hypercortisolism

American Association of Clinical Endocrinologists 26th Annual Scientific and Clinical Congress, Austin, TX, May 5th, 2017

- Speaker for Plenary Session, F51: Practical Issues for Nurse Practitioners/Physician Assistants in an Endocrine Practice, "The Spectrum of Autoimmune Endocrinopathies"

Taking Control of Your Diabetes (TCOYD), Del Mar, CA, November 19th, 2016

- Speaker at the 2016 Orlando Regional Conference on Diabetes, Cardiovascular, and Renal Effects

American Association of Clinical Endocrinologists 25th Annual Scientific and Clinical Congress, Orlando, FL, May 2016

- Covert Cushing's Syndrome – Treating the Deleterious Effects of Cortisol Excess Through Receptor Antagonism

2014 Association of American Medical Colleges Integrating Quality: Improving Value through Clinical Transformation, Education, and Science Meeting, Rosemont, IL, June 2014

- Why Aren't We Reporting? Attitudes and Perceptions of Training Housestaff to Patient Safety Reporting

83rd Annual Meeting of the American Thyroid Association, San Juan, Puerto Rico, October 2013

- Cribriform–Morular Variant of Papillary Thyroid Carcinoma (CMVPTC): Revisiting a 17 Year Old Case with a New Histopathological Diagnosis

The Endocrine Society's 95th Annual Meeting & Expo, San Francisco, CA, June 2013

- Denosumab (Xgeva®) Induced Severe Hypocalcemia in a Metastatic Castration Resistant Prostate Cancer (CRPC) Patient

American Association of Clinical Endocrinologists 22nd Annual Scientific and Clinical Congress, Phoenix, AZ, May 2013

- PEG-Asparaginase (PEG-ASP) Induced Hyperglycemia in a Patient with Acute Lymphoblastic Leukemia (ALL)

Navy Chapter of The American College of Physician Poster Presentation, October 2008
- Hypersensitivity Pneumonitis after Exposure to DOT 5 Silicone Brake Fluids

Grand Rounds and University Invited Presentations

Division of Endocrinology, Diabetes, & Metabolism at The University of California, Davis, Sacramento, CA
- Clinical Consequences of Hypercortisolism – May 3rd, 2018

Division of Endocrinology, Diabetes, & Metabolism at University of Michigan, Ann Arbor, MI
- Medical Therapy for the Treatment of Hypercortisolism – March 22nd, 2018

Division of Endocrinology, Diabetes, & Metabolism at University of California, San Francisco, Fresno, CA
- Internal Medicine Board Review (Endocrinology) – January 2015
- Bone Health and Osteoporosis (Endocrinology) – May 2015

Division of Endocrinology, Diabetes, & Metabolism Grand Rounds at University of Florida
- Endocrine Management of Prader–Willi Syndrome – April 2014
- Internal Medicine Board Review (Endocrinology), Adrenal Disorders – April 2014
- Internal Medicine Board Review (Endocrinology), Thyroid Disorders – April 2014
- Use of Exendin 9–39 to Correct Post-Gastric Bypass Hypoglycemia – March, 2014
- Quarterly Morbidity & Mortality Report – September 2013
- Endocrine Emergencies: Thyroid Storm – August 2013
- Endocrine Emergencies: Hypercalcemia – July 2013
- Amiodarone Thyroid Disorders – July 2013
- Basics of Insulin Pump Therapy – July 2013
- Update on Testosterone Replacement Therapy – June 2013
- Diabetes Spectrum: Maturity Onset Diabetes of the Young – May 2013
- Genetic Connection Between Colorectal and Thyroid Cancer – March 2013
- Familial Heterozygous Hyperlipidemia – February 2013
- Molecular Approach to Thyroid Cancer – October 2012
- Diabetes Spectrum: Latent Autoimmune Diabetes in Adults – September 2012
- Antithyroid Medication Induced Agranulocytosis – August 2012

Grants Awarded

- Kaiser Permanente/Institute for Healthcare Improvement Scholarship, December 2013
- The American Thyroid Association Trainees' Grant Program, July 2013
- American Association of Clinical Endocrinologist Travel Grant, April 2013
- The Endocrine Society's 95th Annual Meeting Early Career Forum Award, February 2013

Honorarium & Consultant Role

Corcept Therapeutics Inc., Menlo Park, CA
- Serving on the content development steering committee on Cushing Syndrome
- Serving on National Medical Advisory Board on Adrenal Adenoma, Cushing Syndrome, and Cushing's Disease

- Serving as a consultant and speaker on treatment of Cushing Syndrome with mifepristone (Korlym®)

Genzyme Corp., Cambridge, MA
- Served as advisor on treatment for homozygous familial hypercholesterolemia (HoFH) with mipomersen sodium

Endo Pharmaceuticals (Endo International Plc), Malvern, PA
- Served as advisor on treatment for male hypogonadism with testosterone undecanoate

Bibliography and Reviewership

- Yau, H, Kinaan M, Quinn SL, Moriatis AG. Octreotide long-acting repeatable in the treatment of neuroendocrine tumors: patient selection and perspectives. *Biologics: Targets & Therapy*. 2017 Dec 6; 11: 115–122.
- Medina Encarnacion D, Vieira D, Kinaan M, Yau H, Quinn Martinez S. Familial Hypercholesterolemia (FH) due to an Uncommon LDL Receptor Mutation. *Integrative Clinical Cardiology*. 2017; 1(1)
- Kinaan M, Yau H, Martinez S, Kar P. Concepts in Diabetic Nephropathy: From Pathophysiology to Treatment. *Journal of Renal and Hepatic Disorders*. 2017; 1(2): 10–24.
- Yau H, Stacpoole P. "*The pathophysiology of hypoglycemia and lactic acidosis in malaria.*" Encyclopedia of Malaria, Ed. Marcel Hommel, Ed. Peter Kremsner. New York: Springer, 2014.
- Yau H, Rivera K, Lomonaco R, Cusi K. The future of thiazolidinedione therapy in the management of type 2 diabetes mellitus. *Curr Diab Rep*. 2013 Jun; 13(3): 329–41.
- Editorial Reviewer for book chapter titled "Partial Remission (honeymoon phase) in Type 1 Diabetes Mellitus: What Clinicians Need to Know" in *Frontiers in Clinical Drug Research - Diabetes and Obesity*, Bentham Science Publishers, UAE. Expected publication 2017.

Civic Activities

The MAVEN Project, 2015 – Present
- Volunteer endocrinology consultant through telemedicine for California clinics devoted to underserved populations

Canine Companion for Independence, 2008 – Present
- Work to increase outreach and placement of exceptional functional canine for the disabled

Habitat for Humanity, 2005 – Present
- Work as part of building teams to construct new homes to eliminate poverty housing nationally

Prior Work Experiences

Senior Quality Control Analyst (June 2000 – July 2001)
Genentech, Inc., South San Francisco, CA

Senior Staff Research Associate (September 1997 – June 2000)

Veterans Affairs Medical Research Foundation in conjunction with the Department of Surgery, University of California, San Diego, CA

Others

Additional training:

- AACE Fundamentals and Advanced Coding – September 2012
- AACE Thyroid FNA and Diagnostic Cytology for Endocrinologist and Advances in Thyroid Cancer Diagnosis and Therapy – January 2012
- AACE Nuclear Medicine Course – August 2011
- Certified insulin pump trainer and prescriber – Medtronics Inc., 2010
- AACE Diagnostic Neck Ultrasound and UGFNA Course – September 2009

FDA REMS Registered Prescriber:

- Parathyroid hormone (Natpara) – primary hypoparathyroidism
- Testosterone Undecanoate (Aveed) – male hypogonadism
- Metreleptin (Myalept) – leptin deficiency in generalized lipodystrophy
- Vandetanib (Caprelsa) – advanced medullary thyroid cancer
- Phenterime/Topiramate (Qsymia) – weight loss
- Mipomersen (Kynamro) – familial hypercholesterolemia
- Lomitapide (Juxtapid)– familial hypercholesterolemia
- Dofetilide (Tikosyn) – highly symptomatic atrial fibrillation/atrial flutter
- Isoretinoin (Accutane) – severe recalcitrant nodular acne
- Etonogestrel (Nexplanon/Implanon) – fertility prevention

References

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I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on July 18, 2018.

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Jo Ann Honcik Dallara/
Jo Ann Honcik Dallara

PATENT
Attorney Docket No.: 085178-1053027-011410US
Client Ref. No.:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Confirmation No.: 2957
Joseph K. Belanoff	Examiner: Chris E. Simmons
Application No.: 15/627,359	Technology Center/Art Unit: 1629
Filed: June 19, 2017	
For: CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A OR STEROIDOGENESIS INHIBITORS	SECOND RULE 132 DECLARATION BY DR. HANFORD K.S. YAU
Customer No.: 144579	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

I, Dr. Hanford K.S. Yau, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true. The Exhibits (1-8) attached to my earlier Rule 132 Declaration dated June 19, 2018 are incorporated herein by reference.

2. I received a medical doctorate from the New York Medical College in 2005, and received fellowship training in Endocrinology, Diabetes and Metabolism at the University of Florida, College of Medicine from 2012-2014. I am board certified in Internal Medicine and in

Endocrinology, Diabetes, and Metabolism by the American Board of Internal Medicine. I am a fellow of the American College of Endocrinology and the American College of Physicians and I hold faculty positions at both the University of Central Florida and at the University of California San Francisco (Fresno Division). I have a clinical practice where I routinely treat Cushing's syndrome patients. I am familiar with modern medical treatments for patients with Cushing's syndrome. My *curriculum vitae* is attached as Exhibit 1.

3. I have read the subject application USSN 15/627,359, the outstanding final Office Action dated June 12, 2018 and the prior art references cited by the Examiner (Korlym® 2012 Package Insert, WO 2009/050136 Ulmann and Kaeser (2009)). I understand that the Examiner believes the pending claims to be obvious over the Package Insert as a primary reference with Ulmann as a secondary reference.

4. My first declaration submitted to the USPTO on June 28, 2018 for USSN 15/627,368, is submitted along with this second declaration to provide evidence of surprising advantages sufficient to traverse the outstanding rejection. This second declaration is intended to provide evidence of how a practicing physician would read and understand the 2012 Package Insert with knowledge of Ulmann and Kaeser. In brief, it appears that the Examiner has interpreted the Package Insert in a manner that contradicts the plain meaning of the language. His reasoning conflates the general instructions for optimizing mifepristone doses in the absence of CYP3A inhibitors with express instructions not to exceed 300 mg/day of mifepristone when combining mifepristone with CYP3A inhibitors. In addition, the Examiner urges that Ulmann is motivation for an artisan to act contrary to the express instructions of the Package Insert. Ulmann teaches that mifepristone can be combined with cortisol synthesis inhibitors including ketoconazole to prevent spikes in cortisol levels attributed to mifepristone. Ulmann does not address the effect of co-administration of ketoconazole on mifepristone levels. Kaeser is addressed in my first Rule 132 Declaration at section 7a, page 8.

5. As I read the outstanding Office Action, the Examiner repeatedly states that an artisan, a doctor treating patients with Korlym®, reading the 2012 Package Insert and the 2009 Ulmann patent application would have understood or have been motivated to dose mifepristone in 300

mg increments up to 1200 mg/day when combined with CYP3A inhibitor. This statement is repeated at pages 6 - 8 of the final Office Action:

> One of ordinary skill in the art would have found it obvious to treat hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome with a composition containing mifepristone and ketoconazole. The artisan would have understood that both mifepristone and ketoconazole are taught to be used for treating Cushing' s diseases and may be combined for that purpose (Ulmann). When combined, the artisan would have further recognized that a "reduction of mifepristone may be required". Thus, if the Cushing' s patient is treated with 1200 mg or 900 mg as disclosed by the package insert and it is found to be beneficial to combine with ketoconazole, then **the artisan would have understood that the concentration of mifepristone may be adjusted by 300 mg increments and as tolerated (see package insert).**
>
> While the prior art does not specifically lower mifepristone dosage to 300 mg and titrating it up to 600 mg, one of ordinary skill in the art would have understood that while lowering it to 300 mg is the more preferred dose of mifepristone when combine with ketoconazole, **the artisan would have recognized that the dose should be adjusted as tolerated while considering the benefits and costs for using the combination of drugs for treatment.**
>
> As outlined above, the package insert teaches that the adjustment of dose of mifepristone based on clinical tolerance and clinical response. Thus, one of ordinary skill in the art would have understood that while lowering it to 300 mg is the more preferred dose of mifepristone when combine with ketoconazole, **the artisan would have recognized that the dose should be adjusted as tolerated while considering the benefits and costs for using the combination of drugs for treatment.**

In the above text, the Examiner has conflated the 2012 Package Insert's general instructions concerning dose titration with the express statements in the Label not to exceed 300 mg/day when mifepristone is combined with a CYP3A inhibitor. In doing so, the Examiner supports his rejection on a misreading of the Package Insert directly contradicting its plain meaning.

6. When combined with CYP3A inhibitors, the label expressly states that the dose of mifepristone should not exceed 300 mg/ml. See page 1 of Exhibit 2 – Package Insert:

> • CYP3A inhibitors: Caution should be used when Korlym is used with strong CYP3A inhibitors. Limit mifepristone dose to 300 mg per day when used with strong CYP3A inhibitors (5.6, 7.2).

The above text is expressly informing physicians not to exceed 300 mg/day of mifepristone when combined with CYP3A inhibitors. This express directive clearly supplants the general directions

to up-titrate dosing of mifepristone from 300 to 1200 mg/day to optimize patient. From Page 1 of the Package Insert:

> **----------DOSAGE AND ADMINISTRATION----------**
>
> * Administer once daily orally with a meal (2).
> * The recommended starting dose is 300 mg once daily (2).
> * Renal impairment: do not exceed 600 mg once daily.
> * Mild-to-moderate hepatic impairment: do not exceed 600 mg once daily. Do not use in severe hepatic impairment.
>
> Based on clinical response and tolerability, the dose may be increased in 300 mg increments to a maximum of 1200 mg once daily. Do not exceed 20 mg/kg per day (2).

FDA approved Package Inserts are recommendations for good medical practice. Practicing physicians, such as myself, view Package Inserts as important guidelines for treating their patients. While physicians are legally permitted to go *off label*, they do so at their own risk of legal liability. In my experience, this is a rare event and most commonly occurs for alternative, non-approved medical indications. It is one thing to prescribe a drug for an off-label use at generally accepted safe doses. It is quite another to treat a patient with drug doses that are counter to the express warnings of the label. This is especially true when those warnings are presenting clear and obvious concerns over toxicity.

While the Ulmann (2009) reference suggests a reason to combine mifepristone with inhibitors of cortisol synthesis including ketoconazole, the 2012 FDA Package Insert is a legally mandated and FDA approved document. Its primary purpose is patient safety. When the Package Insert is read in combination with the teachings of Ulmann (2009), the combination would not motivate a competent physician of ordinary skill to combine more than 300 mg/day of mifepristone with a CYP3A inhibitor including ketoconazole in an attempt to optimize the benefits of mifepristone.

7. As a clinician who has treated patients with Cushing's disease with mifepristone and for the reasons stated above, I respectfully submit that the Examiner's reasoning for rejecting the pending claims goes well beyond the plain meaning of the 2012 Package Insert and is not how an

artisan of ordinary skill would interpret the text of the Package Insert even with knowledge of Ulmann.

The Declarant has nothing further to say.

Hanford K.S. Yau 07/16/2018

Dr. Hanford K.S. Yau Date

Referenced Attachments: Exhibit 1 – Dr. Yau's CV
Exhibit 3 – 2012 FDA Korlym Label

KILPATRICK TOWNSEND & STOCKTON LLP

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on June 28, 2018

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Jo Ann Honcik Dallara/
Jo Ann Honcik Dallara

PATENT
Attorney Docket No.: 085178-1053029-011420US
Client Ref. No.:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Confirmation No.: 3411
Joseph K. Belanoff	Examiner: Barbara P. Badio
Application No.: 15/627,368	Technology Center/Art Unit: 1628
Filed: June 19, 2017	
For: CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A OR STEROIDOGENESIS INHIBITORS	RULE 132 DECLARATION BY DR. PAUL G. PEARSON
Customer No.: 144579	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

I, Dr. Paul G Pearson, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true. The Exhibits (1-8) attached hereto are incorporated herein by reference.

2. I received a doctorate in Pharmacology from the Aston University, Birmingham, England in 1986, held a post-doctoral position at the University of Washington and have held supervisorial positions in the pharmaceutical industry where I focused on drug metabolism. I am presently president and CEO of Pearson Pharma Partners which is a drug discovery and development organization specializing in pharmacokinetics and drug metabolism and

translational medicine strategic and technical guidance for biotechnology and "Pharma" companies. The subject patent owner, Corcept Therapeutics, Inc is a current client of Pearson Pharma Partners. My *curriculum vitae* is attached as Exhibit 1.

3. In the course of my work for Corcept, I have become familiar with their mifepristone product Korlym®, its pharmacokinetics and pharmacodynamics. I have read the subject application USSN 15/627,368, the outstanding non-final Office Action dated March 16, 2018 and the prior art reference cited by the Examiner (WO 2009/050136 (Ulmann). I understand that the Examiner believes the pending claims to be obvious over Ulmann.

The purpose of this declaration is to provide objective evidence of surprising advantages sufficient to traverse the outstanding rejection.

4. THE INVENTION

The pending claims recite a dosing regimen for treating Cushing's syndrome with a combination of mifepristone and a CYP3A inhibitor. The specifics of the claimed invention require that original amount of mifepristone in the absence of the CYP3A inhibitor be reduced by at least 25% to a dose that is greater than **800** mg/day when combined with the CYP3A inhibitor. This claim stands in contrast to the FDA original maximum dose of no greater than **300** mg/day when combined with ketoconazole, which is a strong CYP3A inhibitor that is often used to treat patients with Cushing's syndrome. Pending claim 1 reads:

> 1. A method of treating Cushing's syndrome in a patient who is taking a once daily (OD) dose of mifepristone comprising reducing the once-daily dose amount of said mifepristone administered to said patient from an original OD mifepristone dose amount to an adjusted OD mifepristone dose amount that is greater than 800 mg and is at least 25% less than said original OD mifepristone dose amount when the patient is receiving concomitant administration of a CYP3A inhibitor selected from ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole, cobicistat, danoprevir, elvitegravir indinavir, paritaprevir ombitasvir dasabuvir and troleandomycin.

The outstanding obviousness rejection is over Ulmann (WO 2009/0501136). Ulmann teaches the combination of glucocorticoid receptor antagonists (*eg.* mifepristone) and cortisol

synthesis inhibitors (*eg.* ketoconazole) to treat patients with Cushing's syndrome. The Examiner finds the claimed invention to be *prima facie* obvious.

As discussed below, based on my professional experience, I find the claimed invention to be unexpected and to provide advantages to patients with Cushing's syndrome and doctors treating them.

5. BACKGROUND

Cushing's syndrome is defined by the overproduction of cortisol. It is a life-threatening disorder typically caused by a tumor. The tumor either produces cortisol or adrenocorticotropic hormone (ACTH). ACTH causes the adrenal glands to produce cortisol. By binding to the glucocorticoid receptor (GR), cortisol performs many essential physiological functions. Cortisol also binds to the mineralocorticoid receptor (MR). Significant cortisol binding at MR occurs when cortisol levels are very high.

The abnormally high levels of cortisol in patients with Cushing's syndrome result in excessive activity at the GR, which causes the symptoms of Cushing's syndrome. These symptoms include hyperglycemia, hypertension, persistent infections, hypokalemia, bone loss, hirsutism, psychosis, depression, hirsutism and other adverse effects. The median life expectancy of untreated patients with severe Cushing's syndrome is approximately five years.

Treating patients with Cushing's syndrome presents complex clinical challenges. Surgery to remove the tumor that is secreting excess cortisol or ACTH is the preferred treatment, but is successful in only 50 percent of patients. In the remaining 50 percent of patients, physicians use drugs to reduce cortisol activity.

Before the FDA's approval of mifepristone to treat Cushing's syndrome in 2012, the standard of care was to administer cortisol synthesis inhibitors such as ketoconazole. An undesired side effect of ketoconazole is to strongly inhibit CYP3A. CYP3A is a family of enzymes responsible for the metabolism (i.e., breakdown and clearance) of mifepristone.

Modernly, physicians can use mifepristone (Korlym®) to treat patients with Cushing's syndrome. Mifepristone works by a different mechanism than ketoconazole. Rather than lowering cortisol levels, mifepristone reduces the level of cortisol activity by competing for cortisol at cortisol's primary binding site – GR. As the level of cortisol activity at the GR drops, the symptoms of patients with Cushing's syndrome improve.

In animal models, cardiotoxicity and hepatoxicity were observed with high doses of mifepristone. Following oral intake in humans, mifepristone is extensively metabolized by demethylation and hydroxylation, the initial metabolic steps are catalyzed by the cytochrome P450 (CYP) enzyme CYP3A4. The three most proximal metabolites of mifepristone, namely the monodemethylated, didemethylated and hydroxylated metabolites of mifepristone, all retain considerable affinity toward glucocorticoid receptors. Mifepristone excretion is mainly fecal with less than 10% of the dose recovered in the urine. Based on the available evidence, the FDA did not approve mifepristone in doses higher than 1200 mg/day.

As explained in detail below, patients with Cushing's syndrome are susceptible to fungal, viral, and bacterial infections. They often suffer from depression. Among the drugs used to treat these secondary medical conditions are those that selectively inhibit CYP3A. Until the subject invention was discovered, good medical practice did not recommend combining drugs that inhibit CYP3A with mifepristone. This was because of concern that co-administration would raise mifepristone blood concentrations to toxic levels.

In addition to combining drugs to treat secondary medical disorders associated with Cushing's syndrome, there is motivation to combine ketoconazole with mifepristone to treat the primary condition of Cushing's syndrome – overproduction of cortisol. By antagonizing the GR, mifepristone inhibits the normal feedback loop for cortisol and causes cortisol levels to increase further in many patients. As cortisol levels rise, cortisol binding at MR becomes more frequent and this can result in dangerously low potassium levels – a serious adverse event known as hypokalemia. Hypokalemia is a side effect experienced by approximately 40 percent of the patients taking mifepristone to treat Cushing's syndrome.

Concerned that CYP3A inhibition would lead to dangerously high levels of mifepristone, the FDA limited the recommended dose of mifepristone to 300 mg/day for patients also receiving strong CYP3A inhibitors such as ketoconazole. This is in contrast to the FDA allowing mifepristone doses of up to 1200 mg/day in patients not receiving a strong CYP3A inhibitor. As explained below, doses of mifepristone at or below 300 mg/day give rise to serious questions of therapeutic effectiveness. In the clinical trials presented in the subject application, it was surprisingly determined that mifepristone can be safely combined with CYP3A inhibitors at doses recognized by the medical community as effective. This discovery has significant advantages to patients.

6. COMBINING CYP3A INHIBITORS AND MIFEPRISTONE

Patients with Cushing's syndrome patients are immune suppressed. They benefit from the co-administration of mifepristone and with drugs that are strong CYP3A inhibitors. For example, doctors may wish to administer antibiotics that are strong CYP3A inhibitors to treat bacterial infections. Examples include clarithromycin and telithromycin. Other strong CYP3A inhibitors such as ketoconazole and itraconazole are commonly prescribed to treat fungal, viral, and yeast infections. The CYP3A inhibitor, cimetidine is prescribed to treat heartburn and ulcers. Notably, the combination of ketoconazole, a drug that inhibits cortisol production and mifepristone, a drug that both blocks cortisol action at the GR and elevates cortisol levels can alleviate a patient's symptoms of Cushing's syndrome via two different mechanisms of action. Ketoconazole reduces levels of cortisol and mifepristone reduce the impact of cortisol on the GR. Normalizing cortisol activity at the GR while preventing cortisol levels from spiking has the advantage of reducing the probability of adverse events stemming from cortisol binding at MR, *ie.* hypokalemia.

Despite the various motivations to combine drugs with mifepristone and prior to the surprising clinical findings that support the subject patent application, physicians would have been unlikely to treat Cushing's syndrome with combinations of drugs having CYP3A inhibition with mifepristone because they assumed (wrongly, as it turns out), that inhibition of CYP3A would cause mifepristone levels to become dangerously high.

The fears of the FDA and persons of skill were understandable. When an inhibitor of the CYP3A enzyme (such as ketoconazole) is combined with a drug selectively metabolized by that enzyme (such as mifepristone), toxic levels of the second drug can quickly develop. It is an unpredictable phenomenon because some drugs are metabolized by only CYP3A and others are metabolized by multiple members of the P450 CYP family, or have other compensatory elimination mechanisms. If selectively metabolized by CYP3A, drug levels can increase to between 7 and 20 times the levels that would be observed if in the absence of the CYP3A inhibitor. We can call this dramatic spike in drug levels, the *Greenblatt effect,* named after one of the investigators who has studied the phenomenon with different drugs (Exhibit 2, Greenblatt and Harmatz, 2015).

To ensure that the Greenblatt effect as it relates to combining CYP3A inhibitors and mifepristone did not endanger patients, the FDA instructed doctors to limit mifepristone to doses of no more than 300 mg/day when combined with ketoconazole or other strong CYP3A inhibitors (See Exhibit 3, 2012 Korlym FDA label). A strong CYP3A inhibitor is defined by the FDA to cause a greater than five-fold increase in exposure of the victim drug. The FDA also required Corcept to test for the Greenblatt effect in healthy adults using a combination of mifepristone and ketoconazole. The FDA stated that "only a clinical trial (rather than a nonclinical or observational study) will be sufficient to characterize the effect of co-administration of strong CYP3A inhibitors on increasing mifepristone drug levels and to assess the potential for the known serious risks of severe hypokalemia and adrenal insufficiency." See Exhibit 4, 2012 FDA Approval Letter for NDA 202107 (signed February 17, 2012).

7. SURPRISING ADVANTAGES

Surprisingly, the FDA-mandated clinical study showed that the combination of mifepristone and ketoconazole did not result in dangerously high levels of mifepristone. The Greenblatt effect was not observed. Mifepristone levels increased by only about 25%. The clinical data is presented in the subject patent application.

The failure to observe the Greenblatt effect was surprising, unpredictable and very advantageous to the Cushing's patient population. These results allowed Corcept to devise a method for administering the drugs in combination – with the clinical benefits described above – without risking the toxicity associated with excessive mifepristone levels.

Had the Greenblatt effect occurred (increasing mifepristone levels between 7 and 20 times), physicians could only have prescribed the drugs together by greatly reducing the dose of mifepristone to about 100 mg/day or less – to well below even the FDA's permitted maximum of 300 mg. At such low mifepristone doses, it is extremely unlikely that patients would have experienced any benefit.

7(a). The Greenblatt effect is unpredictable

The impact of ketoconazole on the AUC and Cmax of a co-administered drug varies with the drug being studied,some drugs are sensitive substrates for CYP3A inhibition (>5-fold increase in exposure in the presence of a strong CYP3A inhibitor) some are not. It ranges from

inconsequential changes to increases that are so toxic that the FDA does not recommend combining the drugs under any conditions.

The label for Nizarol (ketoconazole) includes a table of drugs that are known to have toxicity issues when combined with ketoconazole. See Exhibit 5.

Table 1: Selected Drugs That Have Been Shown To or Are Predicted To Have Their Plasma Concentrations Altered By NIZORAL®*

Systemic exposure to these drugs is increased significantly by the addition of ketoconazole. Concomitant use with ketoconazole is contraindicated.	
Alprazolam, midazolam, triazolam	HMG-CoA reductase inhibitors (lovastatin, simvastatin)
Cisapride	Nisoldipine
Dofetilide	Pimozide
Eplerenone	Quinidine
Ergot alkaloids (ergotamine, dihydroergotamine)	
Systemic exposure to these drugs is increased by ketoconazole. Careful monitoring, with possible adjustment in dosage, is recommended.	
Alfentanil, fentanyl, sufentanil	Indinavir, saquinavir
Amlodipine, felodipine, nicardipine, nifedipine	Methylprednisolone
Bosentan	Rifabutin
Buspirone	Sildenafil
Busulfan	Sirolimus (co-administration not recommended)
Carbamazepine	Tacrolimus
Cilostazol	Telithromycin
Cyclosporine	Tolterodine
Digoxin	Trimetrexate
Docetaxel, paclitaxel	Verapamil
Oral anti-coagulants	Vinca alkaloids (vincristine, vinblastine, vinorelbine)

In the text below, there is objective evidence of the unpredictability of the Greenblatt effect.

Midazolam, an anti-anxiolytic benzodiazepine demonstrated an 11.5 fold increase. (See Exhibits 2 and 4)

> Co-administration of NIZORAL® Tablets with alprazolam, midazolam, or triazolam has resulted in elevated plasma concentrations of these drugs. This may potentiate and prolong hypnotic and sedative effects, especially with repeated or chronic administration of these agents. Concomitant administration of NIZORAL® Tablets with alprazolam, oral midazolam, and oral triazolam is contraindicated. (See CONTRAINDICATIONS and WARNINGS sections.) Special precaution and patient monitoring are required with concomitant parenteral midazolam, because the sedative effect may be prolonged.

Exhibit 2, Greenblatt and Harmatz (2015) reported that co-administration with ketoconazole increased midazolam plasma levels by over 11 fold. See Figure 1 on page 344:

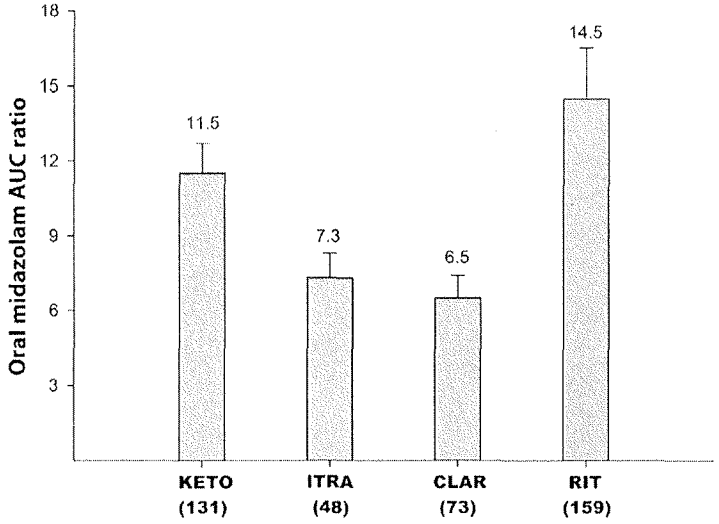


Figure 1

Ratios of total area under the curve (AUC) for oral midazolam during co-administration of each of four inhibitors divided by AUC in the control condition with no inhibitor. Each bar is the mean (±SE) value across studies for the indicated inhibitor, as described in Table 1. KETO ketoconazole, ITRA itraconazole, CLAR clarithromycin, RIT ritonavir. Numbers in parentheses are the total number of subjects participating in studies of the indicated inhibitor

Not all drugs exhibit the Greenblatt effect. See exhibit 6, Kaeser *et al.* (2009) where the antivirals, saquinavir and ritonavir were not excessively elevated when combined with ketoconazole. From page 612 of Kaeser:

TABLE 3. Summary of pharmacokinetic parameters for saquinavir and ritonavir in study arm 1 (n = 20)[a]

Parameter	Saquinavir			Ritonavir		
	GM (%CV)		GMR (90% CI)	GM (%CV)		GMR (90% CI)
	Period 1 (+ ritonavir)	Period 2 (+ ritonavir + ketoconazole)		Period 1 (+ saquinavir)	Period 2 (+ saquinavir + ketoconazole)	
C_{max} (μg/ml)	5.91 (51.5)	5.10 (36.3)	1.02 (0.86–1.20)	1.53 (39.4)	1.66 (26.4)	1.08 (0.96–1.21)
AUC_{0-12} (μg · h/ml)	9.04 (55.3)	8.2 (40.3)	1.07 (0.92–1.26)	8.9 (50.3)	9.95 (30.3)	1.12 (1.03–1.22)
C_{12} (μg/ml)	0.956 (56.3)	1.13 (62.4)	NA	0.230 (57.1)	0.292 (52.7)	NA
T_{max} (h)	3.0 (2.0–6.0)	3.0 (2.0–5.0)	NA	4.0 (2.0–5.0)	4.0 (1.0–5.0)	NA
$t_{1/2}$ (h)	4.9 (3.1–5.9)	5.2 (4.5–6.8)	NA	3.7 (3.1–5.6)	4.2 (3.5–5.3)	NA
CL_s/F (liter/h)	33.4 (55.3)	25.6 (45.3)	NA	11.2 (50.3)	8.7 (32.8)	NA

[a] GMR, geometric mean ratio of period 2 versus 1; GM, geometric mean; NA, not assessed.

Other drugs exhibiting the Greenblatt effect are:

Nisoldipine, a calcium ion blocker with a 24 fold increase (See Exhibit 5)

> Pre-treatment with and concomitant administration of ketoconazole resulted in a 24-fold and 11-fold increase in mean AUC and Cmax of nisoldipine, respectively, compared with treatment with nisoldipine 5 mg alone. **Concomitant administration of ketoconazole with nisoldipine is contraindicated**.

Cisapride, a serotonin 5-HT receptor agonist had an 8 fold increase (See Exhibit 5):

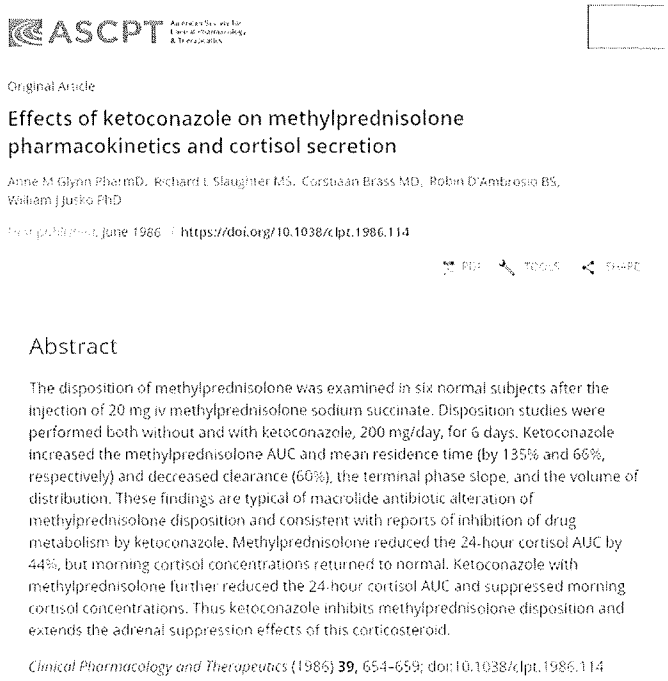
> Oral ketoconazole potently inhibits the metabolism of cisapride resulting in a mean eight-fold increase in AUC of cisapride, which can lead to prolongation of QT interval. Therefore concomitant administration of NIZORAL® Tablets with cisapride is contraindicated

The effect of ketoconazole is *not* predictable as between different steroids.

Eplerenone, a steroidal, antimineralocorticoid is reported to increase by 5 fold (See Exhibit 5)

> Ketoconazole increases the eplerenone AUC by roughly 5-fold, thereby increasing the risk for hyperkalemia. Co-administration of NIZORAL® and eplerenone is contraindicated

Methylprednisolone is increased by 134% See abstract of Glynn et al. 1986:



ASCPT

Original Article

Effects of ketoconazole on methylprednisolone pharmacokinetics and cortisol secretion

Anne M Glynn PharmD, Richard L Slaughter MS, Corstiaan Brass MD, Robin D'Ambrosio BS, William J Jusko PhD

June 1986 | https://doi.org/10.1038/clpt.1986.114

Abstract

The disposition of methylprednisolone was examined in six normal subjects after the injection of 20 mg iv methylprednisolone sodium succinate. Disposition studies were performed both without and with ketoconazole, 200 mg/day, for 6 days. Ketoconazole increased the methylprednisolone AUC and mean residence time (by 135% and 66%, respectively) and decreased clearance (60%), the terminal phase slope, and the volume of distribution. These findings are typical of macrolide antibiotic alteration of methylprednisolone disposition and consistent with reports of inhibition of drug metabolism by ketoconazole. Methylprednisolone reduced the 24-hour cortisol AUC by 44%, but morning cortisol concentrations returned to normal. Ketoconazole with methylprednisolone further reduced the 24-hour cortisol AUC and suppressed morning cortisol concentrations. Thus ketoconazole inhibits methylprednisolone disposition and extends the adrenal suppression effects of this corticosteroid.

Clinical Pharmacology and Therapeutics (1986) **39**, 654–659; doi:10.1038/clpt.1986.114

7(b). The therapeutic benefit of mifepristone at low doses is unpredictable and would require additional clinical studies

The discovery that the Greenblatt effect did not occur when mifepristone is combined with ketoconazole allows Cushing's syndrome patients to use mifepristone at proven therapeutic levels when combined with strong CYP3A inhibitors.

Had the Greenblatt effect applied, and mifepristone levels risen by 7-20 times when combined with a strong CYP3A4 inhibitor, physicians could not have adapted by simply reducing the dose of mifepristone proportionally – from 300 mg per day, for example, to 15-40 mg per day. Achieving therapeutically beneficial plasma levels of mifepristone depends on the amount of mifepristone available to bind GR. When it enters the blood stream, mifepristone is strongly bound by α-1-acid glycoprotein (AAG, also known as orosomucoid). High-affinity binding by AAG removes much of the free mifepristone in plasma, rendering it unavailable to bind GR. An appropriate dose of mifepristone must provide enough drug to overcome AAG binding and provide free drug to bind at GR. Because AAG binding absorbs a significant and

unpredictable portion of a 300 mg mifepristone dose, it is unlikely that a lower dose would have any benefit to patients.

In the seminal clinical study, Exhibit 7 - Fleseriu *et al.* (2012) that led to the approval of mifepristone for the treatment of Cushing's syndrome. The authors wrote on page 2042, column 1:

> The most common doses among responders at wk 24/ET were 600 mg (40%) and 1200 mg (40%), followed by 300 mg (13.3%) and 900 mg (6.7%).

In real world clinical practice, the arithmetic average dose of mifepristone to effectively control Cushing's syndrome is just over 800 mg/day.

If the Greenblatt effect had been observed causing mifepristone blood levels to dramatically increase, the FDA's original recommendation of no more than 300 mg/day would have had to be lowered by another 3-fold to 100 mg/day or less. At those low doses, the capacity of a patient's AAG to bind mifepristone would have been controlling of therapeutic effect because at low doses, the mifepristone would have been mostly bound by the AAG and unavailable to antagonize at its target, GR.

In summary, low doses of mifepristone are therapeutically ineffective due to AAG binding. The binding of mifepristone to AAG means that physicians could not have simply reduced the dose of mifepristone and have expected a therapeutic response by patients with Cushing's syndrome. Even at the FDA's originally required maximum dose of 300 mg/day, it is unclear that the therapeutic benefits of mifepristone would be observed in a majority of patients when co-administered with a strong CYP3A inhibitor.

At a minimum, additional clinical studies would have had to be conducted to determine whether low doses of mifepristone in the presence of ketoconazole or other CYP3A inhibitor were clinically effective and safe. Because low levels of mifepristone of $\leq$300 mg/day were known to be ineffective for the majority of patients with Cushing's syndrome, the therapeutic profile of mifepristone in patients would have had to be established for those patients in need of combination therapy. To do otherwise would have been medically unethical. Such studies

would have cost tens of millions of dollars and delayed the availability of mifepristone for this patient group for 3-5 years.

Fortunately and surprisingly, the results presented by Applicants in the subject application demonstrate that mifepristone is not subject to the Greenblatt effect. There is only about a 25% increase in blood levels of mifepristone in the presence of ketoconazole. This means that the claimed methods, requiring a 25% reduction in the original mifepristone dose when administered in the presence of CYP3A inhibitors like ketoconazole, provide safe and therapeutically effective levels of mifepristone. The claimed invention allows for immediate relief for patients with Cushing's syndrome who would benefit from taking both drugs.

The FDA recognized the importance of the study presented in the subject application; based on this new data, in 2017 the FDA revised the 2012 label to allow a dose of mifepristone in the presence of a strong CYP3A inhibitor that is double the originally recommended dose (Exhibit 9).

> • *Use of Strong CYP3A Inhibitors:* Concomitant use can increase mifepristone plasma levels. Use only when necessary and limit mifepristone dose to 600 mg (5.6).

A further increase in the recommended dose is anticipated by Corcept, based on the new research findings described in the instant patent application.

8. The present methods allow for treatment of other conditions while treating Cushing's syndrome

As stated above, patients suffering from Cushing's syndrome often suffer from other diseases or conditions as well. The suppression of the immune system caused by excess cortisol make patients susceptible to infections. For example, fungal infections (for which ketoconazole, itraconazole, voriconazole, and posaconazole are typically prescribed) are common in Cushing's syndrome patients. Cushing's syndrome patients often suffer from ulcers or other gastrointestinal disorders (for which cimetidine, a CYP3A inhibitor, may be prescribed). Doctors may wish to prescribe strong CYP3A inhibiting antibiotics such as clarithromycin and telithromycin to treat bacterial infections. Cushing's syndrome patients often suffer depression, which appears to be causally related to their high cortisol levels. The antidepressant nefazodone is a strong CYP3A

inhibitor. Prior to the applicant's work and per the warnings and precautions in the FDA label, Cushing's syndrome patients requiring more than 300 mg/day mifepristone could not safely be prescribed any of the strong CYP3A inhibitors commonly prescribed to treat secondary conditions often observed in patients with Cushing's syndrome.

The novel methods of the claims, based on the surprising results disclosed in this application, allow for the concomitant use of CYP3A inhibitors with up to 900 mg/day mifepristone. Thus, the methods of the pending claims provide surprising advantages to the patient with Cushing's syndrome, by providing additional treatment options previously unavailable to those patients requiring more than 300 mg mifepristone per day. Finally, the discovery embodied in the subject claims permits patients to safely combine drugs without the years of delay that would have been required had the Greenblatt effect been observed and low dose clinical trials mandated to assure the clinical effectiveness of low doses of mifepristone when combined with CYP3A inhibiting drugs.

The Declarant has nothing further to say.

Paul B Pearson

Paul Pearson, Ph.D.

Attachments: Exhibit 1 – Dr. Pearson's CV
Exhibit 2 – Greenblatt and Harmatz (2015)
Exhibit 3 – 2012 FDA Korlym Label
Exhibit 4 – 2012 FDA Approval Letter
Exhibit 5 – Nizoral Label
Exhibit 6 – Kaeser et al., (2009)
Exhibit 7 – Fleseriu *et al.* (2012)
Exhibit 8 – 2017 Revised FDA Korlym Label

KILPATRICK TOWNSEND & STOCKTON LLP

EXHIBIT 1 – CV of Dr. Paul G. Pearson

Pearson Pharma Partners

Pharmacokinetics & Drug Metabolism

PAUL G. PEARSON, Ph.D. – President & CEO

Paul G Pearson, Ph.D.
President & CEO
Pearson Pharma Partners,
31194 La Baya Drive, Suite 101
Westlake Village,
California 91362

Office Phone:	650-308-4526
Mobile	805-217-8857
E-mail:	pearson@p3pharma.com

PROFESSIONAL PROFILE

Established leader in Pharmacokinetics and Drug Metabolism (PKDM) with a track record of successfully building and leading industry-recognized PKDM organizations at top pharmaceutical (Merck & Co.) and biotechnology (Amgen) companies.

Corporate-level review board oversight for research and development efforts in discovery and development of small molecule and large molecule human therapeutics.

Twenty-seven years of preclinical and clinical experience in the discovery and development of small molecule and large molecule human therapeutics. Highly experienced in early development activities and strategies to establish proof of biological concept in humans with efficient use of resources.

PHARMA AND BIOTECHNOLOGY LEADERSHIP POSITIONS

President & CEO, Pearson Pharma Partners (May 2008 to present)

A drug discovery and development organization specializing in Pharmacokinetics and Drug Metabolism and Translational Medicine strategic and technical guidance for biotechnology and "Pharma" companies, and venture Capital firms. Current biotechnology clients include companies and VC firms in Boston, Seattle, San Diego and San Francisco bay area. Additional partners include NIH Blueprint Neuroscience Drug (NIH) drug discovery program.

Vice President and Global Head, Pharmacokinetics and Drug Metabolism, Amgen Inc., Thousand Oaks, CA. (Oct 2003- April 2008).
Programmatic responsibility for Pharmacokinetics and Drug Metabolism activities in support of Amgen Inc.'s drug discovery and drug development programs in Thousand Oaks, CA, San Francisco, CA, Boston, MA and Seattle, WA. Direction of 270 scientific personnel engaged in the discovery and development of small molecule and protein therapeutics with an $ 85 MM annual operating budget.

PHARMA AND BIOTECHNOLOGY LEADERSHIP POSITIONS (cont.)

Executive Director, Preclinical Drug Metabolism, Merck Research Laboratories, Merck & Co, Inc., West Point, PA. (Jan 1998 – Sept 2003).

Programmatic responsibility for Preclinical Drug Metabolism activities in support of Merck Research Laboratories drug discovery and drug development programs in West Point, PA and Rahway, NJ. These activities include support to drug discovery efforts at the two largest Merck sites and all Preclinical Drug Metabolism activities in support of Merck development programs. Direction of 160 scientific personnel.

Director, Drug Metabolism, Pharmacia and Upjohn, Kalamazoo, MI.

Held positions of increasing responsibility for Drug Metabolism activities at Upjohn/Pharmacia and Upjohn from 1990-1998. Direction of 40 scientific personnel.

CAREER HIGHLIGHTS

Vice President and Global Head, Pharmacokinetics and Drug Metabolism, Amgen Inc., Thousand Oaks, CA. (Oct 2003- April 2008). Responsibile for Pharmacokinetics and Drug Metabolism activities in support of Amgen Inc.'s drug discovery and drug development programs in Thousand Oaks, CA, San Francisco, CA, Boston, MA and Seattle, WA. These activities include support to small molecule and large molecule drug discovery efforts and all Clinical PK and Preclinical Drug Metabolism activities in support of Amgen's development programs. Between 2003 and 2007, I built the PKDM organization from a group of 135 staff in Thousand Oaks, CA to a global organization of 270 personnel with fully functional PKDM groups at Amgen's research sites in Seattle, Boston, San Francisco and Thousand Oaks. During this period, new laboratory functions were established, high quality leaders and key personnel were hired. New lab space was designed and constructed at all sites and new lab equipment (approx $ 50MM in value) was purchased and installed. Strategic plans were established to successfully build a fully functional, highly integrated global organization with Centers of Excellence in Structural Elucidation, Transporter Technologies, Protein MS analysis and Pharmacometrics. During my tenure, PKDM also managed the integration of personnel and projects from the acquistion of five companies (Tularik, Abgenix, Avidia, Alantos and Ilypsa). My responsibilities included, direction of up to 270 scientific personnel including 70 Ph.D., and numerous MS/BS level scientists in support of Amgen discovery and development programs in hematology, oncology, neuroscience, metabolic disease and bone biology. During my tenure, numerous new drug candidates were introduced into development, including monoclonal antibodies, small molecules, fusion proteins, peptibodies, therapeutic proteins, pegylated peptides directed at a broad range of molecular targets in the therapeutic areas listed above. Successful product approvals include cinacalcet (Sensipar/Mimpara), palifermin (Kepivance), panitumumab (Vectibix – US and EU), and pending US approval of romiplostin (Nplate).

Executive Director, Preclinical Drug Metabolism, Merck Research Laboratories, Merck & Co, Inc., West Point, PA. (Jan 1998 – Sept 2003) Programmatic responsibility for Preclinical Drug Metabolism activities in support of Merck Research Laboratories drug discovery and drug development programs in West Point, PA and Rahway, NJ. These activities include support to drug discovery efforts at the two largest Merck sites and all Preclinical Drug Metabolism activities in support of Merck development programs. Direction of 160 scientific personnel including 50 Ph.D., and numerous MS and BS level scientists; specific technology platforms include, qualitative and quantitative mass spectrometry, NMR spectroscopy, in vitro metabolism systems, extensive range of molecular tools. Participation in Merck Drug Metabolism Council to harmonize global ADME practices at Merck sites in North America, Europe and Japan.

Updated: June 2018

CAREER HIGHLIGHTS (cont.)

Personal accomplishments include: introduction of contemporary LC-MS-MS techniques; acquisition of state-of-the-art NMR technology; leader of ADME subteams to support high priority discovery efforts; coauthor of numerous IND and NDA applications; numerous interactions with global regulatory authorities to support product registration and active participation in FDA Advisory Committee meetings - including approval of caspofungin (Cancidas). I served as the Co-chair of the first Merck Early Development Team (EDT) as part of a new paradigm in accelerated drug development at Merck and also served as co-chair of the clinical Product Development Team (PDT) for this program. The goal of the first EDT was the accelerated development of HIV integrase inhibitors, at that time a new mechanism for treating HIV infections; during my tenure, the team introduced three compounds into development, the first was introduced into clinical trials and established proof of concept in HIV patients with a reduction of viral load to undetectable levels in 5 days. The team also conducted extensive mechanistic toxicology studies to resolve issues associated with copper accumulation and hepatotoxicity in dogs with the early clinical candidates. The results of these efforts established the path for the identification and development of raltegravir (Isentress) as a safe and highly efficacious HIV integrase inhibitor.

Corporate Leadership: Member Merck Safety Assessment Review Committee (1998-2003); member Merck Preclinical Development Review Committee (PRDC; 2003); Preclinical co-chair of first Merck Early Development Team; Co-chair of Product Development Team for a high profile fast-moving development program; member Early Development Team Implementation Committee; member PDRC design team; established strategy and optimal organizational alignment of Preclinical Drug Metabolism organization to meet needs of MRL; conducted long range planning, including facility and succession planning to meet growth needs of Drug Metabolism and Preclinical Development. Member Amgen Discovery Review Board, Amgen Early Development Review Board and Amgen Development Review Board.

RESEARCH EXPERIENCE AND INTERESTS

- Applications of liquid chromatography-mass spectrometry (LC-MS) and tandem mass spectrometry (MS-MS) techniques for the rapid quantitative and qualitative analysis of drugs and drug metabolites.

- Application of in vitro metabolism techniques to elucidate the enzymatic basis for metabolic clearance of drugs in preclinical animal models and humans. Prospective application of in vitro metabolism data to predict clinically-relevant pharmacokinetic based drug-drug interactions.

- Application of drug metabolism to facilitate the discovery of drug candidates with pharmacokinetic properties consistent with their intended therapeutic use. Alteration of metabolism by informed structural modification to optimize pharmacokinetic characteristics.

- Elucidation of the role of chemically-reactive drug metabolites in drug-induced toxicities. Interpretation of metabolism data to provide insights into the mechanism by which xenobiotics exert their potential toxic or carcinogenic effects. Alteration of metabolism/bioactivation by informed structural modification designed to circumvent reactive metabolite formation. Application of stable isotopes (^{2}H, ^{13}C, ^{15}N and ^{18}O) as mechanistic probes to elucidate the nature of transient intermediates in metabolic pathways.

- Application of Pharmacometrics (PK/PD Modeling) for optimization of Clinical Development Programs and establishing therapeutic proof of concept in humans.

PROFESSIONAL EXPERIENCE

Oct 2003- April 2008	Vice President and Global Head Pharmacokinetics and Drug Metabolism Amgen Inc., MS 30E-2-C One Amgen Center Drive Thousand Oaks, CA, 91320
Jan 1998- Sept 2003	Executive Director Preclinical Drug Metabolism, Department of Drug Metabolism, Merck Research Laboratories, Merck & Co. Inc., WP75A-206 West Point, PA, 19486, U.S.A.
June 1997-Jan 1998	Director Drug Metabolism and Disposition Research, Pharmacia and Upjohn, Inc. Kalamazoo, MI 49001, U.S.A.
Jan 1995-May 1997	Associate Director Drug Metabolism Research, The Upjohn Company, Kalamazoo, MI 49001, U.S.A.
June 1992-Dec 1994	Senior Research Scientist Drug Metabolism Research, The Upjohn Company, Kalamazoo, MI 49001, U.S.A.
May 1990-May 1992	Research Scientist II Drug Metabolism Research, The Upjohn Company, Kalamazoo, MI 49001, U.S.A.
Aug 1982-Oct 1982	Resident Pharmacist, Westminster Hospital. Horseferry Road, London SW1 2AP.
Aug 1981-Aug 1982	Pre-registration Pharmacist, Westminster Hospital, Horseferry Road, London SW1 2AP.
Aug 1980-Oct 1980	Synthetic Chemist, Department of Pharmaceutical Sciences, Aston University, Birmingham B4 7ET, England. Synthesis of novel pyrimidines as potential antitumour agents.

EDUCATION

1978-1981 Department of Pharmaceutical Sciences,
Aston University, Birmingham B4 7ET, England.
B.Sc. Pharmacy (2nd Class Honors, upper division)

D.J. Rushton Prize for undergraduate honors project:
"A photoaffinity label for the dinitrophenol binding site of bovine serum albumin".

1982-1985 MRC Mechanisms of Drug Toxicity Research and Cancer Research Campaign Groups
Department of Pharmaceutical Sciences,
Aston University, Aston Triangle, Birmingham, B4 7ET, England.

Ph.D. Scholarship from the Royal Pharmaceutical Society of Great Britain
Ph.D. Thesis title: The Metabolism and Hepatotoxicity of *N*-Methylformamide; awarded 8th January 1986. Ph.D. supervisors: Professor A. Gescher and Dr. E.S. Harpur.

1986-1990 Post-doctoral Research Associate,
Department of Medicinal Chemistry, BG-20,
School of Pharmacy,
University of Washington,
Seattle, Washington 98195, U.S.A.

Principal Investigator - Prof. S.D. Nelson

MEMBERSHIP OF PROFESSIONAL BODIES

1982 Royal Pharmaceutical Society of Great Britain
1985 British Association for Cancer Research
1988 American Society for Mass Spectrometry
1990 American Chemical Society
1993 International Society for the Study of Xenobiotics
2002 International Society for the Study of Xenobiotics, Scientific Affairs Committee
2007 American Society for Clinical Pharmacology and Therapeutics

ACADEMIC AND PROFESSIONAL HONORS

D.J. Rushton Prize for undergraduate honors project, 1981
Ph.D Scholarship from the Royal Pharmaceutical Society of Great Britain. 1986

SUPERVISION OF POSTDOCTORAL FELLOWS

Gregory L. Weber, Ph.D., June 1991 - April 1993
Mohamed El Mouelhi, M.D., Ph.D., September 1992 - July 1994
Larry C. Weinkers, Ph.D., September 1993 - July 1995
Robert T. Streeper, Ph.D., March 1993 - November 1994

INVITED LECTURES:

"The Biliary tree: A target for chemically-induced injury and proliferation", *The Toxicologist*, **14**, 12, 1994

American Association of Pharmaceutical Scientists, Midwest Regional Meeting, Chicago, Il, 1995.

Ninth Lake Louise Workshop on Tandem Mass Spectrometry. Lake Louise, Alberta, Canada, 1996.

International Isotope Society, Tenth Central US Meeting, Indianapolis, IN, 1997

The 6th International Symposia on the Synthesis and Applications of Isotopically Labeled Compounds. Philadelphia, PA, 1997.

Inaugural Land of Lakes Bioanalytical Conference. Devils Head, Merrimac, WI, June 2000

PhRMA/FDA workshop, Washington, DC, A Case Study on the Metabolism of Tirilazad in Preclinical Safety Assessment Species and Humans, November 14-15, 2000

Drew University, Princeton, NJ Chemically-reactive drug metabolites: Implications for drug Design "Designing Safe Drugs: Integration of Disposition Studies in Drug Discovery" June 28-29, 2001.

Gordon Research Conference, Holderness, NH, "Evaluation of Reactive Metabolites in Drug Candidate Selection" July 9-13, 2001

University of Michigan, Department of Pharmacology, School of Medicine. "Evaluation of Reactive Metabolites in Drug Candidate Selection". November 2002

Drew University, Madison, NJ Chemically-reactive drug metabolites:Implications for Drug Design "Designing Safe Drugs: Integration of Disposition Studies in Drug Discovery" June 19-20, 2003.

ISSX North American Meeting, Short-Course: Structural Elucidation of Drug Metabolites, Nov 2003, Providence Rhode Island (course organizer).

ISSX North American Meeting, "Reactive Drug Metabolites in Drug Discovery", Nov 2003, Providence, Rhode Island.

ISSX North American Meeting, Short Course on Metabolite Identification, Nov 2003, Providence, Rhode Island.

University of Washington, School of Pharmacology, "Biotechnology Course". "Denosumab: Potential to Remodel the Future of Bone Therapy". August 2006

University of Washington, School of Pharmacology, "Biotechnology Course". "Denosumab in Osteoporosis and Oncology: Discovery to Development". August 2007

University of California, San Francisco, University of California, School of Pharmacy,The Impact of Pharmacokinetics in Modern Drug Development—10 Years Later. *"Blood, Bone and Biology: Pharmacokinetics in Development of Human Therapeutic Agents. November, 17-18, 2007.*

INVITED LECTURES (Cont.):

ISSX North American Meeting, Short-Course: ADME Properties of Protein Therapeutics, October 2008, San Diego, California (course organizer).

ISSX North American Meeting, Symposium: Successful Development of Biotherapeutics: Scientific and Regulatory Strategies and Hurdles for Toxicology and ADME/PK. October 2008, San Diego, California (symposium co-chair).

Alcon Laboratories: PKDM Biotherapeutics Course. April 30-May 1, 2009, Fort Worth, Texas (2 day course on preclinical and clinical development of biological-based therapeutics).

Ascent Therapeutics: PKDM Course. October 5, 2009, Cambridge, MA (1 day course on Pharmacokinetics Drug Metabolism and Preclinical Development).

Alkermes: Biotherapeutics Course. May 17, 2010, Cambridge, MA (1 day course on preclinical and clinical development of biological-based therapeutics).

Alkermes: Small Molecule PKDM Course. May 19, 2010, Cambridge, (1 day course on Pharmacokinetics Drug Metabolism and Preclinical Development).

BOOKS

P.G. Pearson and L.C. Wienkers, eds. Handbook of Drug Metabolism. 2nd Edition. Informa Healthcare, New York, NY. 2008.

P.G. Pearson and L.C. Wienkers, eds. Handbook of Drug Metabolism. 3rd Edition. Informa Healthcare, New York, NY. 2018 – in press.

PUBLICATIONS, ABSTRACTS AND CONFERENCE PRESENTATIONS

ABSTRACTS

1. **P.G. Pearson**, A. Gescher and E.S. Harpur. Studies in mice of the association of metabolites of N-methylformamide with hepatic macromolecules. *Human Toxicol.*, **3**, 328-329 (1984).

2. **P.G. Pearson**, A. Gescher and E.S. Harpur. Activation of N-methylformamide by liver microsomes of Balb/c mice to a covalently bound species. *Human Toxicol.*, **4**, 548-549 (1985).

3. A. Gescher, E.S. Harpur and **P.G. Pearson**. Strain differences in the hepatotoxicity of N-methylformamide in mice. *Brit. J.Pharmacol.*, **86**, 514P (1985).

4. A. Gescher, E.S. Harpur, P. Kestell and **P.G. Pearson**. Strain differences in the metabolism of N-methylformamide in mice. *Brit. J.Pharmacol.*, **86**, 515P. (1985).

5. **P.G. Pearson**, E.S. Harpur and A. Gescher. *In vitro* covalent binding of N-methylformamide: relationship to hepatotoxicity. *Fd.Chem.Toxic.*, **24**, 814 (1986).

6. **P.G. Pearson**, M.D. Threadgill, A. Gescher and E.S. Harpur. The protective role of glutathione in the hepatotoxicity of N-methylformamide in Balb/c mice. *Human Toxicol.*, **5**, 147-148 (1986).

7. **P.G. Pearson**, I.S. Pratt, A. Gescher and E.S. Harpur. Pathological changes in the livers of Balb/c mice induced by N-methylformamide. Presented at The European Society of Toxicology Meeting, Harrogate, England (1987).

8. J.H.N. Meerman, **P.G.Pearson**, G.P. Meier and S.D. Nelson. The formation of four cyclic 1,N^2-(hydroxy-bromo-)-propanodeoxyguanosine isomers from the reaction of 2-bromoacrolein with deoxyguanosine. *Proc. Am. Assoc. Can. Res.* **28,** 404 (1987)

9. J.G. Omichinski, R.H. McClanahan, **P.G. Pearson**, E.J. Soderlund, E. Dybing and S.D. Nelson. Usage of radioisotopes and stable isotopes to investigate the metabolism of tris-BP to reactive intermediates. Presented at the Third Stowe School Symposium on Drug Metabolism (1987).

10. **P.G. Pearson**, W.N. Howald, M.D. Threadgill and T.A. Baillie. Applications of Tandem Mass Spectrometry to the characterization of derivatized glutathione conjugates. *Proceedings of the 36th ASMS Conference on Mass Spectrometry and Allied Topics* , 458-459 (1988).

11. T.A. Baillie, **P.G. Pearson**, M.D. Threadgill, W.N. Howald, D.-H. Han and N. E. Mackenzie. Stable Isotopes: Unique probes for mechanistic studies of xenobiotic metabolism. *2nd International ISSX Meeting " Xenobiotic Metabolism and Disposition"* Kobe, Japan (1988).

12. M.D. Threadgill, T.A. Baillie, P.B. Farmer, A. Gescher, P. Kestell and **P.G. Pearson.** Primary deuterium kinetic isotope effects on the metabolism of N-methylformamide in mice. *International Journal of Applied Isotopes* (in press)

13. **P.G. Pearson**. Identification of derivatized glutathione conjugates by tandem mass spectrometry. Presented at a *"Workshop on Hybrid Tandem Mass Spectrometry"*, Lake Louise, Alberta, Canada (1988).

14. **P.G. Pearson**, W.N. Howald, S.D. Nelson and T.A. Baillie. A screening strategy for the detection of derivatized glutathione conjugates by tandem mass spectrometry. *Proceedings of the 37th ASMS Conference on Mass Spectrometry and Allied Topics*, 1322-1323 (1989).

15. **P.G. Pearson** and S.D. Nelson. Bioactivation of 1,2-dibromo-3-chloropropane to five Glutathione Conjugates *in vivo*: Mechanism of formation and detection by tandem mass spectrometry. *Proceedings of the 37th ASMS Conference on Mass Spectrometry and Allied Topics*, 1320-1321 (1989).

16. **P.G. Pearson**, J. G. Slatter, M. S. Rashed, D.-H. Han and T.A. Baillie. Applications of stable isotopes and tandem mass spectrometry to the characterization of reactive metabolite peptide interactions. *Proceedings of the 37th ASMS Conference on Mass Spectrometry and Allied Topics*, 850-851 (1989).

17. D. Thomassen, **P.G. Pearson** and S.D. Nelson. Characterization of the biliary metabolites of the hepatotoxic monoterpene Pulegone by tandem mass spectrometry. *Proceedings of the 37th ASMS Conference on Mass Spectrometry and Allied Topics*, 1326-1327 (1989).

18. M.S. Rashed, R.E. Talaat, **P.G. Pearson** and T.A. Baillie. A facile method for the preparation and LC/MS characterization of benzyloxycarbonyl methyl esters derivatives of reduced glutathione, cysteine and corresponding xenobiotic-thioether conjugates. *Proceedings of the 37th ASMS Conference on Mass Spectrometry and Allied Topics*, 955-956 (1989).

19. R. Dayal, H. Cross, A. Gescher, **P.G. Pearson** and T.A. Baillie. Generation and Toxicity of Thiocarbamate metabolites of *N*-methylformamide (NMF). 2nd International Conference on Practical *in vitro* Toxicology. (Nottingham, England. July 1989)

20. J.G. Slatter, M.S. Rashed, **P.G. Pearson**, D.-H. Han and T.A. Baillie. Characterization of reactive S-linked conjugates of Methylisocyanate in the rat by Tandem Mass Spectrometry and Liquid Chromatography / Mass Spectrometry. Presented at the *Second International Symposium on Mass Spectrometry in the Health and Life Sciences.* (San Francisco, CA. August 27-31, (1989).

21. E.Dybing, E.J. Soderlund, M. Lag, G. Brunborg, J.A. Holme, **P.G. Pearson** and S.D. Nelson. Mechanism of 1,2-dibromo-3-chloropropane (DBCP) nephrotoxicity. 'Mechanisms of Tissue Specific Toxicity' (November 1989, Wurzberg, F.R. Germany).

22. **P.G. Pearson**. Metabolic activation of haloalkanes by conjugation with glutathione. Canadian Society for Mass Spectrometry *"International Workshop on Hybrid Tandem Mass Spectrometry and High Performance 3 or 4 Sector MS-MS"*, Lake Louise, Alberta, Canada (December, 1989).

23. T.A. Baillie, **P.G. Pearson**, J.G. Slater, M.S. Rashed, D.-H. Han, W.N. Howald, R. Dayal, L.H. Tsang and A. Gescher. Glutathione Conjugation in the Transport of Biological Reactive Intermediates. *'4th International Symposium on Biological Biological Reactive Intermediates'* (January 1990, Tuscon, Ariz.).

24. J.G. Slater, M.S. Rashed, **P.G. Pearson**, D.-H. Han and T.A. Baillie. Methyl isocyanate biotransformation in rats: Identification of reactive Glutathione-derived metabolites in bile and urine. *The Toxicologist*, **10**, 200 (1990).

ABSTRACTS (Cont.)

25. J.G. Slatter, M.R. Davis, D.-H. Han, **P.G. Pearson**, and T.A. Baillie. A mass spectrometric investigation of the mechanism of Methylisocyanate release *in vivo* during the metabolism of the experimental antitumor agent Caracemide. *Proceedings of the 38th ASMS Conference on Mass Spectrometry and Allied Topics*, 802-803 (1990).

26. W.N. Howald, L.J. Buck and **P.G. Pearson**. An alternative MS/MS high voltage power supply and display module for a Tandem Hybrid Instrument: VG 70-SEQ. *Proceedings of the 38th ASMS Conference on Mass Spectrometry and Allied Topics,* 569-570 (1990).

27. **P.G. Pearson**, W.N. Howald and S.D. Nelson. Semi-quantitative analysis of derivatized glutathione conjugates by Tandem Mass Spectrometry (MS/MS) with parent ion scanning. *Proceedings of the 38th ASMS Conference on Mass Spectrometry and Allied Topics,* 1507-1508 (1990).

28. **P.G. Pearson**. Analysis of glutathione conjugates by parent ion MS / MS. Canadian Society for Mass Spectrometry *"International Workshop on Hybrid Tandem Mass Spectrometry and High Performance 3 or 4 Sector MS-MS"*, Lake Louise, Alberta, Canada (December, 1990).

29. J.J. Vrbanac, P.E. Sanders, **P.G. Pearson**, R.C. Steenwyk, L.Baczynskyj and I.A. O'Leary. Partial characterization of U-78875 in monkey urine by tandem mass spectrometry. *Proceedings of the 39th ASMS Conference on Mass Spectrometry and Allied Topics,* Nashville, TN. May 20-24, 1991, pp 1683-1684.

30. P.E. Sanders, I.A. O'Leary, J.J. Vrbanac, R.C. Steenwyk and **P.G. Pearson**. Particle beam LC/MS of thermally labile compounds. *Proceedings of the 39th ASMS Conference on Mass Spectrometry and Allied Topics,* Nashville, TN. May 20-24, 1991, pp 1326-1327.

31. **P.G. Pearson**, W.N. Howald, and S.D. Nelson. Identification of glutathione conjugates of 1,2-dibromo-3-chloropropane by tandem mass spectrometry (MS-MS): Application of multiple MS-MS scan modes. Presented at Gordon Research Conference on Drug Metabolism. Holderness, NH, July 15-19, 1991.

32. **P.G. Pearson** and S.D. Nelson. Metabolic Activation of 1,2-dibromo-3-chloropropane: Application of stable isotopes as mechanistic probes. Presented at The 4th International Symposia on the Syntheses and Applications of Isotopically Labeled Compounds. Toronto, Canada, September 1991.

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EXHIBIT 2

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12668

Ritonavir is the best alternative to ketoconazole as an index inhibitor of cytochrome P450-3A in drug–drug interaction studies

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Keywords
clarithromycin, cytochrome P450-3A, drug–drug interactions, itraconazole, ketoconazole, ritonavir

Received
17 March 2015
Accepted
24 April 2015
Accepted Article Published Online
28 April 2015

AIMS
The regulatory prohibition of ketoconazole as a CYP3A index inhibitor in drug–drug interaction (DDI) studies has compelled consideration of alternative inhibitors.

METHODS
The biomedical literature was searched to identify DDI studies in which oral midazolam (MDZ) was the victim, and the inhibitory perpetrator was either ketoconazole, itraconazole, clarithromycin, or ritonavir. The ratios (R_{AUC}) of total area under the curve (AUC) for MDZ with inhibitor divided by MDZ AUC in the control condition were aggregated across individual studies for each inhibitor.

RESULTS
Mean (± SE) R_{AUC} values were: ketoconazole (15 studies, 131 subjects), 11.5 (±1.2); itraconazole (five studies, 48 subjects), 7.3 (±1.0); clarithromycin (five studies, 73 subjects), 6.5 (±10.9); and ritonavir (13 studies, 159 subjects), 14.5 (±2.0). Differences among inhibitors were significant ($F = 5.31$, $P < 0.005$). R_{AUC} values were not significantly related to inhibitor dosage or to duration of inhibitor pre-exposure prior to administration of MDZ.

CONCLUSIONS
Ritonavir produces CYP3A inhibition equivalent to or greater than ketoconazole, and is the best index CYP3A inhibitor alternative to ketoconazole. Cobicistat closely resembles ritonavir in structure and function, and can also be considered. Itraconazole and clarithromycin are not suitable alternatives since they do not produce inhibition comparable with ketoconazole or ritonavir, and have other significant disadvantages as well.

Introduction

The Drug Safety Communication issued by the United States Food and Drug Administration (FDA) in July 2013, warned against and limited the use of oral ketoconazole for systemic antifungal treatment, based on what was stated to be a risk of severe liver injury which could potentially lead to liver transplantation or death [1]. The European Medicines Agency Committee on Medicinal Products for Human Use issued a similar statement at the same time [2]. In October 2013, the FDA followed with a statement recommending against the use of ketoconazole as an index inhibitor of human cytochrome P450-3A (CYP3A) isoforms in clinical drug–drug interaction (DDI) studies [3].

The FDA has not provided the outcome of what they term a comprehensive benefit–risk assessment of the safety and efficacy of oral ketoconazole. Also unavailable

are the results of an independent evaluation of data from the FDA Adverse Event Reporting System (FAERS) by a hepatology expert at the FDA. A review of published literature on ketoconazole-associated liver injury [4], and an external analysis of FAERS reports [5], led to the following conclusions: 1) liver injury associated with ketoconazole is uncommon, 2) when it happens, liver injury is nearly always evident as asymptomatic and reversible alterations in liver function tests, 3) serious liver injury is rare, 4) there is no substantive or consistent evidence that ketoconazole carries a risk of liver injury different from other azole antifungals, and 5) There is negligible evidence of a liver injury risk from ketoconazole used as an index CYP3A inhibitor in DDI studies of healthy volunteers.

Notwithstanding a lack of scientific support, the regulatory decisions still impose a liability burden on clinicians who prescribe ketoconazole for systemic antifungal treatment, and on investigators who use ketoconazole in DDI studies of CYP3A-mediated drug clearance [6]. Reasonable antifungal treatment options are available as alternatives to ketoconazole, but CYP3A inhibitor alternatives for DDI studies in the course of drug development are not so clear.

For a drug candidate suspected of being a CYP3A inhibitor ('perpetrator'), a DDI study using a sensitive CYP3A substrate drug as 'victim' can be performed to determine the candidate's quantitative inhibition potency [7]. Such studies often include a trial arm using a strong CYP3A inhibitor – usually ketoconazole – as a positive control, to compare the inhibitory effect of the candidate drug with the 'worst case scenario'. If the candidate drug itself is a CYP3A substrate, a DDI study using ketoconazole as the inhibitor would map the worst case for the substrate under conditions of maximal CYP3A inhibition.

An appropriate alternative to ketoconazole as a strong index CYP3A inhibitor for DDI studies should produce maximal inhibition of CYP3A activity. Itraconazole, clarithromycin, and ritonavir have been proposed as alternatives [3, 4, 6, 8], but their quantitative inhibitory potency *in vivo* relative to that of ketoconazole has not been established. The present review evaluates published clinical DDI studies in which ketoconazole, itraconazole, clarithromycin, or ritonavir have been used as an index CYP3A inhibitor in clinical DDI studies with oral midazolam as the index substrate.

Methods

A total of 38 studies, involving 411 subjects, were identified through standard procedures for search of published biomedical literature (Table 1). We elected to consider studies of orally administered midazolam, since clearance will reflect activity of both hepatic and enteric CYP3A [10]. The majority of studies evaluated were single dose crossover trials, in which oral midazolam was given in the control state, and again with co-administration of the index inhibitor. The principal outcome variable for this review was the ratio (R_{AUC}) of total area under the plasma concentration curve (AUC) for oral midazolam during co-administration of inhibitor (AUC_I) divided by the AUC in the control condition with no inhibitor (AUC_0), as follows [7]:

$$R_{AUC} = (AUC_I)/(AUC_0)$$

For each study, we recorded the overall mean of individual R_{AUC} values, as provided by the authors in 66 % of the studies. This was not available in 34 % of the studies, in which case we used the mean value of AUC_i divided by mean AUC_0. Also recorded were the daily doses of the inhibitor, the dosage schedule (single or divided daily doses), and the duration of pre-exposure to the inhibitor prior to administration of midazolam.

R_{AUC} values were aggregated as the arithmetic mean across all studies of each inhibitor. Analysis of variance (ANOVA) for independent groups using rank-transformed data was performed to determine the overall significance of differences in R_{AUC} among the four inhibitor categories. For each inhibitor, the relation of R_{AUC} to daily dose of inhibitor and to the duration of inhibitor pre-exposure was evaluated by multiple regression analysis.

Table 1

Summary of oral midazolam drug–drug interaction studies of each inhibitor

Inhibitor	Number of studies	Number of subjects	References	Median (with range) Daily dose (mg)	Pre-exposure duration (days)	Dose schedule: single (S) or divided (D) daily doses
Ketoconazole	15	131	[9–19]	400 (200–400)	3 (0–14)	12S, 3D
Itraconazole	5	48	[9], [20–23]	200 (100–400)	3 (0.17–5)	5S, 0D
Clarithromycin	5	73	[24–28]	1000 (500–1000)	4 (3–7)	0S, 5D
Ritonavir	13	159	[31–40]	200 (100–600)	13 (0–>30)	5S, 12D

For the purpose of this study we did not consider maximum plasma concentration (C_{max}) as an outcome variable, since C_{max} depends on the rate of absorption as well as AUC.

Results

The median duration of pre-exposure to inhibitors ranged from 3 to 13 days (Table 1), with variation of individual values from 0 (the inhibitor given as a single dose concurrently with midazolam) to more than 30 days. Median daily doses were 200 mg for itraconazole and ritonavir, 400 mg for ketoconazole and 1000 mg for clarithromycin. Multiple regression analysis indicated no apparent relationship of R_{AUC} to daily dosage or duration of pre-exposure for any of the inhibitors.

Figure 1 shows overall mean R_{AUC} values for the four inhibitor groups, without weighting of individual mean values for the number of subjects in each study. If means are weighted for sample size, the outcome is essentially identical.

The overall difference among inhibitors was significant ($F = 5.31$, $P < 0.005$). R_{AUC} values for ketoconazole and ritonavir (11.5 and 14.5, respectively) were not significantly different from each other (Student–Newman–Keuls test). Both were significantly larger than values for itraconazole and clarithromycin (7.3 and 6.5), which in turn were not different from each other.

In none of the 15 studies involving ketoconazole as inhibitor were liver function abnormalities reported.

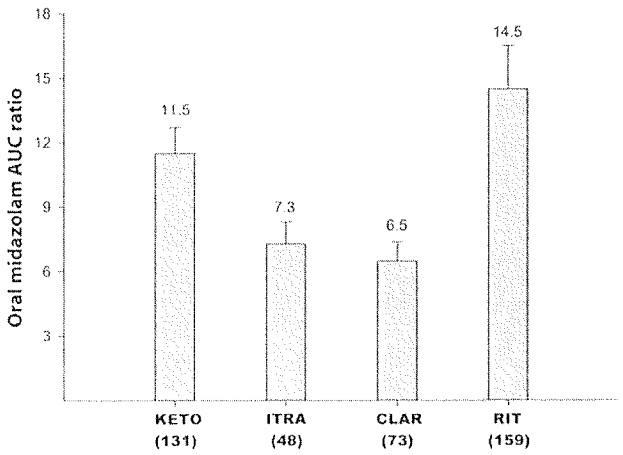

Figure 1

Ratios of total area under the curve (AUC) for oral midazolam during co-administration of each of four inhibitors divided by AUC in the control condition with no inhibitor. Each bar is the mean (±SE) value across studies for the indicated inhibitor, as described in Table 1. KETO ketoconazole, ITRA itraconazole, CLAR clarithromycin, RIT ritonavir. Numbers in parentheses are the total number of subjects participating in studies of the indicated inhibitor

Discussion

The findings indicate that ritonavir produces *in vivo* inhibition of CYP3A metabolic activity that is comparable with or greater than that of ketoconazole. Inhibition by itraconazole and clarithromycin were similar to each other, and both were less than the extent of inhibition produced by ketoconazole or ritonavir. Regulatory guidance classifies inhibitors as 'strong' if they produce R_{AUC} values exceeding 5.0. This qualifies itraconazole and clarithromycin as 'strong' inhibitors, but they do not produce maximal *in vivo* CYP3A inhibition comparable to ketoconazole or ritonavir. As such, itraconazole and clarithromycin are not reasonable alternatives to ketoconazole.

Ketoconazole is well recognized as a CYP3A inhibitor having high inhibitory potency [4, 6, 7, 41–47]. Ketoconazole produces reversible inhibition, with a mechanism that is mixed competitive and non-competitive [46]. Variable *in vitro* inhibition constant (K_i) values for ketoconazole have been reported among a large number of studies, but K_i typically is in the range of 0.05–0.1 μM [42, 47]. This is considerably below the usual range of plasma ketoconazole concentrations during therapeutic use (1–5 μM) [9, 48, 49], and is consistent with the high degree of inhibition observed *in vivo*. Because ketoconazole has a short elimination half-life, steady-state is reached rapidly after initiation of exposure, and no more than 24 h of pre-treatment is needed to produce maximal CYP3A inhibition [17, 50]. The time course of reversibility of ketoconazole inhibition after discontinuation is likely to be rapid as well [51].

Itraconazole also is a reversible CYP3A inhibitor. Usual *in vitro* K_i values are in the range of 0.1–0.5 μM, compared to *in vivo* plasma concentrations of 0.05–1.0 μM [4, 9, 23, 41, 42, 49, 52–55]. Itraconazole has metabolic products with CYP3A inhibitory activity that are likely to contribute to *in vivo* inhibition [23, 53, 54, 56, 57]. Because of the long elimination half-life of itraconazole and its metabolites, there is accumulation with repeated dosage [49, 57–61]. As such, the onset and offset of *in vivo* CYP3A inhibition is slower than what is established for ketoconazole [20, 22].

Clarithromycin is a macrolide derivative that produces time-dependent (mechanism-based) inhibition of CYP3A [62–66]. The inhibitory potency of clarithromycin is considerably less than ketoconazole or ritonavir. Values of the half-maximal inactivation constant or 50% inhibitory concentration (IC_{50}) for clarithromycin *in vitro* are in the range of 2–30 μM [64, 67], compared to plasma concentrations in the range of 2–6 μM [27, 68–70]. As such, the extent of *in vivo* CYP3A inhibition with clarithromycin does not approach what could be considered maximal [4, 8, 67]. As a time-dependent inhibitor [62–66, 71–74], the onset and offset of CYP3A inhibition is likely to be delayed [75]. In a study of erythromycin – also a

macrolide derivative producing time-dependent CYP3A inhibition – the apparent half-life of onset of inhibition following initiation of treatment was calculated to be 22.5 h [76].

Ritonavir is a highly potent CYP3A inhibitor *in vitro*, with a combination of reversible and time-dependent mechanisms [54, 77–80]. Values of K_i or IC_{50} generally are less that 0.2 μM, compared to plasma concentrations in the range of 1.0–10 μM [31, 32, 35, 36, 38, 81]. In clinical studies, the inhibitory potency of ritonavir is at least as great as that of ketoconazole (Fig. 1). CYP3A inhibition by ritonavir is dose- and exposure-dependent [35, 38], but in the majority of studies, daily doses in the typical 'boosting' range of 100 to 200 mg produce maximal or near-maximal inhibition [35, 38, 81–83]. The onset of CYP3A inhibition is rapid following initiation of ritonavir treatment, with maximal inhibition after 2 to 3 days of exposure [31, 35, 82, 83]. In one study of the reversal of inhibition, CYP3A activity reverted to baseline by 4 days after discontinuation of ritonavir dosage at 400 mg day^{-1} [82]. In another study, recovery from CYP3A inhibition was incomplete at 3 days after termination of ritonavir exposure at doses of 300–600 mg daily [35].

Ketoconazole, itraconazole, and ritonavir have inhibitory actions against other human CYP isoforms in addition to CYP3A [41, 42, 77, 78, 84–88]. However the values of K_i or IC_{50} *vs.* isoforms other than CYP3A are at least one order of magnitude higher (lower inhibitory potency) than for CYP3A [42, 77, 78, 88]. In clinical DDI studies, ketoconazole co-administration had minimal effects on the pharmacokinetics of antipyrine, caffeine, theophylline, and chlordiazepoxide [6]. Co-administration of itraconazole with the CYP2D6 substrate drugs aripiprazole [89] and tramadol [90] increased AUC values by factors of 1.48 and 1.11, respectively. In DDI studies involving ritonavir as a CYP inhibitor, short term exposure to boosting doses of ritonavir produced only small or negligible inhibition of clearance of dextromethorphan (CYP2D6) [30], desipramine (CYP2D6) [91], bupropion (CYP2B6) [92], omeprazole (CYP2C19) [37], S-warfarin (CYP2C9) [39] and flurbiprofen (CYP2C9) [37]. In cell culture models, ritonavir produces transcriptional activation and increased expression of a number of CYP isoforms and transport proteins [34, 93–95]. In clinical studies, induction of clearance of substrate drugs such as caffeine (CYP1A2) [95], olanzapine (CYP1A2) [96] and tolbutamide (CYP2C9) [95] has been demonstrated with extended exposure to relatively high doses of ritonavir. However the lower 'boosting' doses produce only small or modest degrees of induction [29]. Taken together, the data suggest that ketoconazole, itraconazole, and ritonavir all have high relative specificity as CYP3A inhibitors. The low dosage range for ritonavir, along with the short exposure durations typical of DDI studies, minimizes concerns about induction effects.

The candidate CYP3A inhibitors all produce some degree of inhibition of transport mediated by P-glycoprotein (ABCB1). This is evident from *in vitro* and experimental studies, as well as clinical DDI studies evaluating enteric uptake, partitioning across the blood–brain barrier, or renal clearance of P-glycoprotein substrates [30, 36, 97–110]. For victim drugs that are potential substrates both for metabolism by CYP3A and transport by P-glycoprotein, the outcome of DDI studies using these candidate inhibitors is likely to reflect concurrent inhibition of both CYP3A and P-glycoprotein.

Cobicistat is closely related to ritonavir in structure and pharmacologic properties [111–113]. Cobicistat has been approved as a single entity agent for pharmacokinetic boosting in antiretroviral therapy. In a DDI study directly comparing the inhibitory effect of 200 mg cobicistat and 100 mg ritonavir on clearance of oral midazolam, the mean R_{AUC} values for midazolam were 19.0 for cobicistat and 23.9 for ritonavir [40]. Like ritonavir, cobicistat is an inhibitor of P-glycoprotein activity [114], and is a relatively, but not completely, specific inhibitor of CYP3A. Both ritonavir and cobistat inhibit CYP2D6 activity *in vitro*, with IC_{50} or K_i values in the range of 3–14 μM [78, 84, 112]. In a clinical DDI study of cobicistat with the CYP2D6 substrate desipramine (as reported in the product label, but not published), cobocistat increased desipramine AUC by a factor of 1.65. Ritonavir increased desipramine AUC by a factor of 1.26 in a similarly-designed DDI trial [91]. The available data on cobicistat suggest that it could serve as an index CYP3A inhibitor for DDI studies. The product label for cobistat indicates that the drug can decrease creatinine clearance due to inhibition of tubular secretion of creatinine without affecting glomerular function. The ritonavir label describes elevations in serum transaminases in patients receiving ritonavir alone, or in combination with other antiretroviral drugs. However there is no evidence that either of these issues is of concern for DDI studies in healthy volunteers with no renal or hepatic disease.

Conclusions

There is no established risk of liver injury when ketoconazole is used as an index CYP3A inhibitor for DDI studies in healthy volunteers. Still, the regulatory action against ketoconazole forces consideration of alternatives. Itraconazole and clarithromycin have been proposed, but neither produces *in vivo* CYP3A inhibition approaching that of ketoconazole. Itraconazole has a long half-life and active metabolites, such that the onset and offset of CYP3A inhibitory activity are delayed. Clarithromycin is a time-dependent (mechanism-based) inhibitor, and its onset and offset of activity also are likely to be delayed. Ritonavir produces rapid onset CYP3A inhibition of magnitude at least as great as ketoconazole, and is the most reasonable alternative. Cobicistat closely resembles ritonavir, and also warrants consideration.

Competing Interests

Both authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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EXHIBIT 3

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Korlym™ safely and effectively. See full prescribing information for Korlym.

Korlym™ (mifepristone) 300 mg Tablets

Initial U.S Approval 2000

WARNING: TERMINATION OF PREGNANCY

See full prescribing information for complete boxed warning.

Mifepristone has potent antiprogestational effects and will result in the termination of pregnancy. Pregnancy must therefore be excluded before the initiation of treatment with Korlym, or if treatment is interrupted for more than 14 days in females of reproductive potential.

----------INDICATIONS AND USAGE----------

Korlym (mifepristone) is a cortisol receptor blocker indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.

Important Limitations of Use (1.1)

- Do not use for the treatment of type 2 diabetes mellitus unrelated to endogenous Cushing's syndrome.

----------DOSAGE AND ADMINISTRATION----------

- Administer once daily orally with a meal (2).
- The recommended starting dose is 300 mg once daily (2).
- Renal impairment: do not exceed 600 mg once daily.
- Mild-to-moderate hepatic impairment: do not exceed 600 mg once daily. Do not use in severe hepatic impairment.

Based on clinical response and tolerability, the dose may be increased in 300 mg increments to a maximum of 1200 mg once daily. Do not exceed 20 mg/kg per day (2).

----------DOSAGE FORMS AND STRENGTHS----------

• 300 mg tablet

----------CONTRAINDICATIONS----------

- Pregnancy (4.1, 8.1)
- Use of simvastatin or lovastatin and CYP 3A substrates with narrow therapeutic range (4.2)
- Concurrent long-term corticosteroid use (4.3)
- Women with history of unexplained vaginal bleeding (4.4)
- Women with endometrial hyperplasia with atypia or endometrial carcinoma (4.4)

----------WARNINGS AND PRECAUTIONS----------

- *Adrenal insufficiency*: Patients should be closely monitored for signs and symptoms of adrenal insufficiency (5.1).
- *Hypokalemia*: Hypokalemia should be corrected prior to treatment and monitored for during treatment (5.2).
- *Vaginal bleeding and endometrial changes*: Women may experience endometrial thickening or unexpected vaginal bleeding. Use with caution if patient also has a hemorrhagic disorder or is on anti-coagulant therapy (5.3).
- *QT interval prolongation*: Avoid use with QT interval-prolonging drugs, or in patients with potassium channel variants resulting in a long QT interval (5.4).
- *Use of Strong CYP3A Inhibitors:* Concomitant use can increase mifepristone plasma levels significantly. Use only when necessary and limit mifepristone dose to 300 mg (5.6).

----------ADVERSE REACTIONS----------

Most common adverse reactions in Cushing's syndrome (≥ 20%): nausea, fatigue, headache, decreased blood potassium, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite, endometrial hypertrophy

To report suspected adverse reactions, contact Corcept Therapeutics at 1-855-844-3270 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

• Drugs metabolized by CYP3A: Administer drugs that are metabolized by CYP3A at the lowest dose when used with Korlym (7.1).
• CYP3A inhibitors: Caution should be used when Korlym is used with strong CYP3A inhibitors. Limit mifepristone dose to 300 mg per day when used with strong CYP3A inhibitors (5.6, 7.2).
• CYP3A inducers: Do not use Korlym with CYP3A inducers (7.3).
• Drugs metabolized by CYP2C8/2C9: Use the lowest dose of CYP2C8/2C9 substrates when used with Korlym (7.4).
• Drugs metabolized by CYP2B6: Use of Korlym should be done with caution with bupropion and efavirenz (7.5).
• Hormonal contraceptives: Do not use with Korlym (7.6).

----------USE IN SPECIFIC POPULATIONS----------

- Nursing mothers: Discontinue drug or discontinue nursing (8.3).

See Section 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide

FULL PRESCRIBING INFORMATION: Contents*

*Sections or subsections omitted from the full prescribing information are not listed

Korlym™ (mifepristone) 300 mg tablets for oral use

FULL PRESCRIBING INFORMATION

WARNING: TERMINATION OF PREGNANCY

Mifepristone is a potent antagonist of progesterone and cortisol via the progesterone and glucocorticoid (GR-II) receptors, respectively. The antiprogestational effects will result in the termination of pregnancy. Pregnancy must therefore be excluded before the initiation of treatment with Korlym and prevented during treatment and for one month after stopping treatment by the use of a non-hormonal medically acceptable method of contraception unless the patient has had a surgical sterilization, in which case no additional contraception is needed. Pregnancy must also be excluded if treatment is interrupted for more than 14 days in females of reproductive potential.

1 INDICATIONS AND USAGE

Korlym (mifepristone) is a cortisol receptor blocker indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.

LIMITATIONS OF USE:

- Korlym should not be used in the treatment of patients with type 2 diabetes unless it is secondary to Cushing's syndrome.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosage

The recommended starting dose is 300 mg orally once daily. Korlym must be given as a single daily dose. Korlym should always be taken with a meal. Patients should swallow the tablet whole. Do not split, crush, or chew tablets.

Dosing and titration

The daily dose of Korlym may be increased in 300 mg increments. The dose of Korlym may be increased to a maximum of 1200 mg once daily but should not exceed 20 mg/kg per day. Increases in dose should not occur more frequently than once every 2-4 weeks. Decisions about dose increases should be based on a clinical assessment of tolerability and degree of improvement in Cushing's syndrome manifestations. Changes in glucose control, anti-diabetic medication requirements, insulin levels, and psychiatric symptoms may provide an early assessment of response (within 6 weeks) and may help guide early dose titration. Improvements in cushingoid appearance, acne, hirsutism, striae, and body weight occur over a longer period of time and, along with measures of glucose control, may be used to determine dose changes beyond the first 2 months of therapy. Careful and gradual titration of Korlym accompanied by monitoring for recognized adverse reactions (*See Warnings and Precautions 5.1 and 5.2*) may reduce the risk of severe adverse reactions. Dose reduction or even dose discontinuation may be needed in some

clinical situations. If Korlym treatment is interrupted, it should be reinitiated at the lowest dose (300 mg). If treatment was interrupted because of adverse reactions, the titration should aim for a dose lower than the one that resulted in treatment interruption.

2.2 Dosing in Renal Impairment

No change in initial dose of Korlym is required in renal impairment. The maximum dose should be limited to 600 mg. *[See Renal Impairment (8.6) and Clinical Pharmacology (12.3)]*

2.3 Dosing in Hepatic Impairment

No change in the initial dose of Korlym is required in mild to moderate hepatic impairment. The maximum dose should be limited to 600 mg. Korlym should not be used in severe hepatic impairment. *[See Hepatic Impairment (8.7) and Clinical Pharmacology (12.3)]*

3 DOSAGE FORMS AND STRENGTHS

Korlym is supplied as a light yellow to yellow oval-shaped tablet debossed with "Corcept" on one side and "300" on the other. Each tablet contains 300 mg of mifepristone. The tablets are not scored.

4 CONTRAINDICATIONS

4.1 Pregnancy

Korlym is contraindicated in women who are pregnant. Pregnancy must be excluded before the initiation of treatment with Korlym or if treatment is interrupted for more than 14 days in females of reproductive potential. Nonhormonal contraceptives should be used during and one month after stopping treatment in all women of reproductive potential. *[See Use in Specific Populations 8.8]*

4.2 Drugs Metabolized by CYP3A

Korlym is contraindicated in patients taking simvastatin, lovastatin, and CYP3A substrates with narrow therapeutic ranges, such as cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, due to an increased risk of adverse events. *[See Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*

4.3 Corticosteroid Therapy Required for Lifesaving Purposes

Korlym is contraindicated in patients who require concomitant treatment with systemic corticosteroids for serious medical conditions or illnesses (e.g., immunosuppression after organ transplantation) because Korlym antagonizes the effect of glucocorticoids.

4.4 Women with Risk of Vaginal Bleeding or Endometrial Changes

Korlym is contraindicated in the following:

- Women with a history of unexplained vaginal bleeding
- Women with endometrial hyperplasia with atypia or endometrial carcinoma

4.5 Known Hypersensitivity to Mifepristone

Korlym is contraindicated in patients with prior hypersensitivity reactions to mifepristone or to any of the product components.

5 WARNINGS AND PRECAUTIONS

5.1 Adrenal Insufficiency

Patients receiving mifepristone may experience adrenal insufficiency. Because serum cortisol levels remain elevated and may even increase during treatment with Korlym, serum cortisol levels do not provide an accurate assessment of hypoadrenalism in patients receiving Korlym. Patients should be closely monitored for signs and symptoms of adrenal insufficiency, including weakness, nausea, increased fatigue, hypotension, and hypoglycemia. If adrenal insufficiency is suspected, discontinue treatment with Korlym immediately and administer glucocorticoids without delay. High doses of supplemental glucocorticoids may be needed to overcome the glucocorticoid receptor blockade produced by mifepristone. Factors considered in deciding on the duration of glucocorticoid treatment should include the long half-life of mifepristone (85 hours).

Treatment with Korlym at a lower dose can be resumed after resolution of adrenal insufficiency. Patients should also be evaluated for precipitating causes of hypoadrenalism (infection, trauma, etc.).

5.2 Hypokalemia

In a study of patients with Cushing's syndrome, hypokalemia was observed in 44% of subjects during treatment with Korlym. Hypokalemia should be corrected prior to initiating Korlym. During Korlym administration, serum potassium should be measured 1 to 2 weeks after starting or increasing the dose of Korlym and periodically thereafter. Hypokalemia can occur at any time during Korlym treatment. Mifepristone-induced hypokalemia should be treated with intravenous or oral potassium supplementation based on event severity. If hypokalemia persists in spite of potassium supplementation, consider adding mineralocorticoid antagonists.

5.3 Vaginal Bleeding and Endometrial Changes

Being an antagonist of the progesterone receptor, mifepristone promotes unopposed endometrial proliferation that may result in endometrium thickening, cystic dilatation of endometrial glands, and vaginal bleeding. Korlym should be used with caution in women who have hemorrhagic disorders or are receiving concurrent anticoagulant therapy. Women who experience vaginal bleeding during Korlym treatment should be referred to a gynecologist for further evaluation.

5.4 QT Interval Prolongation

Mifepristone and its metabolites block IKr. Korlym prolongs the QTc interval in a dose-related manner. There is little or no experience with high exposure, concomitant dosing with other QT-prolonging drugs, or potassium channel variants resulting in a long QT interval. *[See Warnings & Precautions (5.6)]* To minimize risk, the lowest effective dose should always be used.

5.5 Exacerbation/Deterioration of Conditions Treated with Corticosteroids

Use of Korlym in patients who receive corticosteroids for other conditions (e.g., autoimmune disorders) may lead to exacerbation or deterioration of such conditions, as Korlym antagonizes the desired effects of glucocorticoid in these clinical settings. For medical conditions in which chronic corticosteroid therapy is life-saving (e.g., immunosuppression in organ transplantation), Korlym is contraindicated. *[See Contraindications (4.3)]*

5.6 Use of Strong CYP3A Inhibitors

Korlym should be used with extreme caution in patients taking ketoconazole and other strong inhibitors of CYP3A, such as itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, nefazodone, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, or voriconazole, as these could substantially increase the concentration of mifepristone in the blood. The benefit of concomitant use of these agents should be carefully weighed against the potential risks. Mifepristone should be used in combination with strong CYP3A inhibitors only when necessary, and in such cases the dose should be limited to 300 mg per day. *[See Warnings & Precautions (5.4), Drug Interactions (7.2), and Clinical Pharmacology (12.3)]*

5.7 *Pneumocystis jiroveci* Infection

Patients with endogenous Cushing's syndrome are at risk for opportunistic infections such as *Pneumocystis jiroveci* pneumonia during Korlym treatment. Patients may present with respiratory distress shortly after initiation of Korlym. Appropriate diagnostic tests should be undertaken and treatment for *Pneumocystis jiroveci* should be considered.

5.8 Potential Effects of Hypercortisolemia

Korlym does not reduce serum cortisol levels. Elevated cortisol levels may activate mineralcorticoid receptors which are also expressed in cardiac tissues. Caution should be used in patients with underlying heart conditions including heart failure and coronary vascular disease.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

Safety data on the use of Korlym are available from 50 patients with Cushing's syndrome enrolled in an uncontrolled, open-label, multi-center trial (Study 400). Forty-three patients had Cushing's disease and all except one had previously undergone pituitary surgery. Four patients had ectopic ACTH secretion, and three had adrenal carcinoma. Patients were treated for up to 24 weeks. A dose of 300 mg per day was administered for the initial 14 days; thereafter, the dose could be escalated in increments of 300 mg per day based on assessments of tolerability and clinical response. Doses were escalated up to 900 mg per day for patients <60 kg, or 1200 mg per day for patients >60 kg.

The most frequently reported adverse reactions (reported in ≥20% of patients, regardless of relationship to Korlym) were nausea, fatigue, headache, decreased blood potassium, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite, and endometrial hypertrophy. Drug-related adverse events resulted in dose interruption or reduction in study drug in 40% of patients.

The adverse reactions that occurred in ≥10% of the Cushing's syndrome patients receiving Korlym, regardless of relationship to Korlym, are shown in Table 1.

Table 1. Treatment Emergent Adverse Events Occurring in ≥10% of Cushing's Syndrome Patients Receiving Korlym

Body System/Adverse Reaction	Percent (%) of Patients Reporting Event (n = 50)
Gastrointestinal disorders	
Nausea	48
Vomiting	26
Dry mouth	18
Diarrhea	12
Constipation	10
General disorders and administration/site conditions	
Fatigue	48
Edema peripheral	26
Pain	14
Nervous system disorders	
Headache	44
Dizziness	22
Somnolence	10
Musculoskeletal and connective tissue disorders	
Arthralgia	30
Back pain	16
Myalgia	14
Pain in extremity	12
Investigations	
Blood potassium decreased	34
Thyroid function test abnormal	18
Infections and infestations	
Sinusitis	14
Nasopharyngitis	12
Metabolism and nutrition disorders	
Decreased appetite	20
Anorexia	10
Vascular disorders	
Hypertension	24
Reproductive system and breast disorders	
Endometrial hypertrophy	38*
Respiratory, thoracic, and mediastinal disorders	
Dyspnea	16
Psychiatric disorders	
Anxiety	10

*The denominator was 26 females who had baseline and end-of-trial transvaginal ultrasound

6.2 Laboratory Tests

Reductions in high density lipoprotein-cholesterol (HDL-C) levels have been observed following treatment with Korlym. In study subjects that experienced declines in HDL-C, levels returned to baseline following discontinuation of drug. The clinical significance of the treatment-related reduction in HDL-C levels in patients with Cushing's syndrome is not known.

In a study of patients with Cushing's syndrome, hypokalemia was observed in 44% of subjects during treatment with Korlym. In these cases, hypokalemia responded to treatment with potassium supplementation and/or mineralocorticoid antagonist therapy (e.g., spironolactone or eplerenone). Hypokalemia should be corrected prior to initiating Korlym. *[See Warnings and Precautions (5.2)]*

Elevations of thyroid-stimulating hormone (TSH) were seen in subjects treated with Korlym. Of the 42 subjects with detectable TSH at baseline, eight (19%) had increases in TSH above the normal range, while remaining asymptomatic. The TSH levels returned to normal in most patients without intervention when Korlym was discontinued at the end of the study.

6.3 Vaginal Bleeding and Endometrial Changes

In Study 400, the thickness of the endometrium increased from a mean of 6.14 mm at baseline (n=23) to 15.7 mm at end-of-trial (n=18) in premenopausal women; in postmenopausal women the increase was from 2.75 mm (n=6) to 7.35 mm (n=8). Endometrial thickness above the upper limit of normal was reported in 10/26 females who had baseline and end-of-trial transvaginal ultrasound (38%). The endometrial thickness returned to the normal range in 3 out of 10 patients 6 weeks after treatment cessation at the end of the study. Vaginal bleeding occurred in 5 out of 35 females (14%). Two of five subjects with vaginal bleeding had normal endometrial thickness. Endometrial biopsies were performed in six patients; five of these patients had endometrial thickening. No endometrial carcinoma was detected in the sampled cases.

6.4 Additional Data from Clinical Trials

The following are adverse events that were reported in Study 400 at frequencies of ≥ 5% to 10%, and may be related to Korlym's mechanism of action:

Gastrointestinal disorders: gastroesophageal reflux, abdominal pain

General disorders and administration site conditions: asthenia, malaise, edema, pitting edema, thirst

Investigations: blood triglycerides increased

Metabolism and nutrition disorders: hypoglycemia

Musculoskeletal and connective tissue disorders: muscular weakness, flank pain, musculoskeletal chest pain

Psychiatric disorders: insomnia

Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia *[See Warnings and Precautions (5.3)]*

6.4.1 Adrenal Insufficiency

Adrenal insufficiency was reported in two subjects (4%) in Study 400. The most typical symptoms of adrenal insufficiency were nausea and decreased appetite. No hypotension or hypoglycemia was reported

during the events. Adrenal insufficiency resolved in both cases with Korlym interruption and /or dexamethasone administration.

6.4.2 Rash

Generalized, maculo-papular rash was reported in 2 subjects (4%) in Study 400. Two additional subjects developed pruritus (4%). None resulted in discontinuation of Korlym, and all the events resolved by the end of the study.

7 DRUG INTERACTIONS

Based on the long terminal half-life of mifepristone after reaching steady state, at least 2 weeks should elapse after cessation of Korlym before initiating or increasing the dose of any interacting concomitant medication.

7.1 Drugs Metabolized by CYP3A

Because Korlym is an inhibitor of CYP3A, concurrent use of Korlym with a drug whose metabolism is largely or solely mediated by CYP3A is likely to result in increased plasma concentrations of the drug. Discontinuation or dose reduction of such medications may be necessary with Korlym co-administration.

Korlym increased the exposure to simvastatin and simvastatin acid significantly in healthy subjects. Concomitant use of simvastatin or lovastatin is contraindicated because of the increased risk of myopathy and rhabdomyolysis. *[See Contraindications (4.2), Clinical Pharmacology 12.3]*

The exposure of other substrates of CYP3A with narrow therapeutic ranges, such as cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, may be increased by concomitant administration with Korlym. Therefore, the concomitant use of such CYP3A substrates with Korlym is contraindicated. *[See Contraindications (4.2)]*

Other drugs with similar high first pass metabolism in which CYP3A is the primary route of metabolism should be used with extreme caution if co-administered with Korlym. The lowest possible dose and/or a decreased frequency of dosing must be used with therapeutic drug monitoring when possible. Use of alternative drugs without these metabolic characteristics is advised when possible with concomitant Korlym.

If drugs that undergo low first pass metabolism by CYP3A or drugs in which CYP3A is not the major metabolic route are co-administered with Korlym, use the lowest dose of concomitant medication necessary, with appropriate monitoring and follow-up. *[See Clinical Pharmacology (12.3)]*

7.2 CYP3A Inhibitors

Medications that inhibit CYP3A could increase plasma mifepristone concentrations and dose reduction of Korlym may be required.

Ketoconazole and other strong inhibitors of CYP3A, such as itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir and fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, mibefradil, nefazodone, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, or voriconazole may increase exposure to mifepristone significantly. The clinical impact of this interaction has not been studied. Therefore, extreme caution should be used when these drugs are prescribed in

combination with Korlym. The benefit of concomitant use of these agents should be carefully weighed against the potential risks. The dose of Korlym should be limited to 300 mg and used only when necessary. *[See Warnings & Precautions (5.6)]*

Moderate inhibitors of CYP3A, such as amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, or verapamil, should be used with caution when administered in combination with Korlym.

7.3 CYP3A Inducers

No medications that induce CYP3A have been studied when co-administered with Korlym. Avoid co-administration of Korlym and CYP3A inducers such as rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine, and St. John's wort.

7.4 Drugs Metabolized by CYP2C8/2C9

Because Korlym is an inhibitor of CYP2C8/2C9, concurrent use of Korlym with a drug whose metabolism is largely or solely mediated by CYP2C8/2C9 is likely to result in increased plasma concentrations of the drug.

Korlym significantly increased exposure of fluvastatin, a typical CYP2C8/2C9 substrate, in healthy subjects. When given concomitantly with Korlym, drugs that are substrates of CYP2C8/2C9 (including non-steroidal anti-inflammatory drugs, warfarin, and repaglinide) should be used at the smallest recommended doses, and patients should be closely monitored for adverse effects. *[See Clinical Pharmacology (12.3)]*

7.5 Drugs Metabolized by CYP2B6

Mifepristone is an inhibitor of CYP2B6 and may cause significant increases in exposure of drugs that are metabolized by CYP2B6 such as bupropion and efavirenz. Since no study has been conducted to evaluate the effect of mifepristone on substrates of CYP2B6, the concomitant use of bupropion and efavirenz should be undertaken with caution. *[See Clinical Pharmacology (12.3)]*

7.6 Use of Hormonal Contraceptives

Mifepristone is a progesterone-receptor antagonist and will interfere with the effectiveness of hormonal contraceptives. Therefore, non-hormonal contraceptive methods should be used.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Category X

Korlym is contraindicated in pregnancy. Korlym can cause fetal harm when administered to a pregnant woman because the use of Korlym results in pregnancy loss. The inhibition of both endogenous and exogenous progesterone by mifepristone at the progesterone receptor results in pregnancy loss. If Korlym is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. *[See Contraindications (4.1)]*

Human Data

In a report of thirteen live births after single dose mifepristone exposure, no fetal abnormalities were noted.

Animal Data

Teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than human exposure at the maximum clinical dose, based on body surface area) were carried out. Because of the anti-progestational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at less than human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from antagonism of the progesterone receptor.

8.3 Nursing Mothers

Mifepristone is present in human milk of women taking the drug. Because of the potential for serious adverse reactions in nursing infants from Korlym, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of Korlym in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies with Korlym did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger people.

8.6 Renal Impairment

The maximum dose should not exceed 600 mg per day in renally impaired patients. *[See Clinical Pharmacology (12.3)]*

8.7 Hepatic Impairment

In patients with mild to moderate hepatic impairment, the maximum dose should not exceed 600 mg per day. The pharmacokinetics of mifepristone in patients with severe hepatic impairment has not been studied, and Korlym should not be used in these patients. *[See Clinical Pharmacology (12.3)]*

8.8 Females of Reproductive Potential

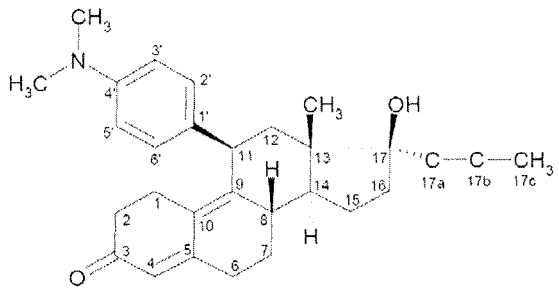
Due to its anti-progestational activity, Korlym causes pregnancy loss. Exclude pregnancy before the initiation of treatment with Korlym or if treatment is interrupted for more than 14 days in females of reproductive potential. Recommend contraception for the duration of treatment and for one month after stopping treatment using a non-hormonal medically acceptable method of contraception. If the patient has had surgical sterilization, no additional contraception is needed.

10 OVERDOSAGE

There is no experience with overdosage of Korlym.

11 DESCRIPTION

Korlym (mifepristone) is a cortisol receptor blocker for oral administration. The chemical name of mifepristone is 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(1-propynyl)-estra-4, 9-dien-3-one. The chemical formula is $C_{29}H_{35}NO_2$; the molecular weight is 429.60; and the structural formula is:



Mifepristone demonstrates a pH-related solubility profile. The greatest solubility is achieved in acidic media (~ 25 mg/mL at pH 1.5) and solubility declines rapidly as the pH is increased. At pH values above 2.5 the solubility of mifepristone is less than 1 mg/mL.

Each Korlym tablet for oral use contains 300 mg of mifepristone. The inactive ingredients of Korlym tablets are silicified microcrystalline cellulose, sodium starch glycolate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate, hypromellose, titanium dioxide, triacetin, D&C yellow 10 aluminum lake, polysorbate 80, and FD&C yellow 6 aluminum lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mifepristone is a selective antagonist of the progesterone receptor at low doses and blocks the glucocorticoid receptor (GR-II) at higher doses. Mifepristone has high affinity for the GR-II receptor but little affinity for the GR-I (MR, mineralocorticoid) receptor. In addition, mifepristone appears to have little or no affinity for estrogen, muscarinic, histaminic, or monoamine receptors.

12.2 Pharmacodynamics

Because mifepristone acts at the receptor level to block the effects of cortisol, its antagonistic actions affect the hypothalamic-pituitary-adrenal (HPA) axis in such a way as to further increase circulating cortisol levels while, at the same time, blocking their effects.

Mifepristone and the three active metabolites have greater affinity for the glucocorticoid receptor (100%, 61%, 48%, and 45%, respectively) than either dexamethasone (23%) or cortisol (9%).

12.3 Pharmacokinetics

Absorption

Following oral administration, time to peak plasma concentrations of mifepristone occurred between 1 and 2 hours following single dose, and between 1 and 4 hours following multiple doses of 600 mg of

Korlym in healthy volunteers. Mean plasma concentrations of three active metabolites of mifepristone peak between 2 and 8 hours after multiple doses of 600 mg/day, and the combined concentrations of the metabolites exceed that of the parent mifepristone. Exposure to mifepristone is substantially less than dose proportional. Time to steady state is within 2 weeks, and the mean (SD) half-life of the parent mifepristone was 85 (61) hours following multiple doses of 600 mg/day of Korlym.

Studies evaluating the effects of food on the pharmacokinetics of Korlym demonstrate a significant increase in plasma levels of mifepristone when dosed with food. To achieve consistent plasma drug concentrations, patients should be instructed to always take their medication with meals.

Distribution

Mifepristone is highly bound to alpha-1-acid glycoprotein (AAG) and approaches saturation at doses of 100 mg (2.5 μM) or more. Mifepristone and its metabolites also bind to albumin and are distributed to other tissues, including the central nervous system (CNS). As determined in vitro by equilibrium dialysis, binding of mifepristone and its three active metabolites to human plasma proteins was concentration-dependent. Binding was approximately 99.2% for mifepristone, and ranged from 96.1 to 98.9% for the three active metabolites at clinically relevant concentrations.

Metabolism

Cytochrome P450 3A4 (CYP3A4) has been shown to be involved in mifepristone metabolism in human liver microsomes. Two of the known active metabolites are the product of demethylation (one monodemethylated and one di-demethylated), while a third active metabolite results from hydroxylation (monohydroxylated).

Elimination and Excretion

Excretion is primarily (approximately 90%) via the fecal route.

Specific Populations

Renal Impairment

The pharmacokinetics of mifepristone in subjects with severe renal impairment (creatinine clearance [CrCL] < 30 mL/min, but not on dialysis) was evaluated following multiple doses of 1200 mg Korlym for 7 days. Mean exposure to mifepristone increased 31%, with similar or smaller increases in metabolite exposure as compared to subjects with normal renal function (CrCL ≥ 90 mL/min). There was large variability in the exposure of mifepristone and its metabolites in subjects with severe renal impairment as compared to subjects with normal renal function (geometric least square mean ratio [CI] for AUC of mifepristone: 1.21 [0.71-2.06]; metabolite 1: 1.43 [0.84-2.44]; metabolite 2: 1.18 [0.64-2.17] and metabolite 3: 1.19 [0.71-1.99]). No change in the initial dose of Korlym is needed for renal impairment; the maximum dose should not exceed 600 mg per day.

Hepatic Impairment

The pharmacokinetics of mifepristone in subjects with moderate hepatic impairment (Child-Pugh Class B) was evaluated in a single- and multiple-dose study (600 mg for 7 days). The pharmacokinetics in subjects with moderate hepatic impairment was similar to those with normal hepatic function. There was large variability in the exposure of mifepristone and its metabolites in subjects with moderate hepatic impairment as compared to subjects with normal hepatic function (geometric least square mean ratio [CI] for AUC of mifepristone: 1.02 [0.59-1.76]; metabolite 1: 0.95 [0.52-1.71]; metabolite 2: 1.37 [0.71-2.62] and metabolite 3: 0.62 [0.33-1.16]). Due to limited information on safety in patients with mild-to-

moderate hepatic impairment, the maximum dose should not exceed 600 mg per day. The pharmacokinetics of mifepristone in patients with severe hepatic disease has not been studied. Korlym is not recommended in patients with severe hepatic disease.

Drug-Drug Interactions

In Vitro Assessment of Drug Interactions

In vitro studies indicate a potential for CYP-mediated drug interactions by mifepristone and/or its metabolites with substrates of CYP2A6, CYP2C8/2C9, CYP2C19, CYP3A4, CYP1A2, CYP2B6, CYP2D6, and CYP2E1. In vitro studies also indicated an interaction potential for drug transport mediated by P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). In vitro studies indicate mifepristone metabolism is mediated by CYP3A, and that mifepristone also inhibits and induces CYP3A.

In Vivo Assessment of Drug Interactions (see Table 2)

Table 2. Summary Table of Korlym Drug-Drug Interaction Effects

Dosing of Mifepristone	Coadministered Drug	Dosing of Coadministered Drug	Geometric Mean Ratio (analyte ratio with/without drug coadministration)		
			Analyte	AUC	Cmax
Effect of Korlym on Coadministered Drug					
Contraindicated with mifepristone *[See Contraindications (4)]*					
1200 mg once daily for 10 days	simvastatin[1]	80 mg single dose	simvastatin acid simvastatin	15.70 10.40	18.20 7.02
Use lowest dose of coadministered drug, based on clinical experience and/or use of therapeutic drug monitoring					
1200 mg once daily for 10 days	alprazolam[2]	1 mg single dose	alprazolam 4-hydroxy-alprazolam	1.80 0.76	0.81 0.39
1200 mg once daily for 7 days	fluvastatin[3]	40 mg single dose	fluvastatin	3.57	1.76
1200 mg once daily for 10 days	digoxin[4]	0.125 mg once daily	digoxin	1.40	1.64
Effect of Coadministered Drug on Korlym					
No dosing adjustment required					
300 mg once daily for 14 days	cimetidine[5]	800 mg once daily	mifepristone	0.85*	0.75

*No effect = 90% CI within range 0.80 – 1.25

[1] Simvastatin 40 mg dose used as reference for the comparison. Result could be representative of other oral drugs with CYP3A metabolism and high first pass effect: cyclosporine, midazolam, triazolam, pimozide, sildenafil, sirolimus, and tacrolimus

[2] Result could be representative of other oral drugs with CYP3A metabolism and low first pass effect. Clinical significance of any interaction will depend on the therapeutic margin of the drug.

[3] Result could be representative of other oral drugs with CYP2C8/C9 metabolism

[4] Plasma digoxin concentration should be measured after 1 to 2 weeks of concomitant use and following usual clinical practice at appropriate intervals thereafter.

[5] Result could be representative of other mild inhibitors of CYP3A

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Mifepristone was evaluated for carcinogenicity potential in rats and mice. Rats were dosed for up to two years at doses of 5, 25, and 125 mg/kg of mifepristone. The high dose was the maximum tolerated dose, but exposure at all doses was below exposure at the maximum clinical dose based on AUC comparison. Female rats had a statistically significant increase in follicular cell adenomas/carcinomas and liver adenomas. It is plausible that these tumors are due to drug-induced enzyme metabolism, a mechanism not considered clinically relevant, but studies confirming this mechanism were not conducted with mifepristone. Mice were also tested for up to 2 years at mifepristone doses up to the maximum tolerated dose of 125 mg/kg, which provided exposure below the maximum clinical dose based on AUC. No drug-related tumors were seen in mice.

Mifepristone was not genotoxic in a battery of bacterial, yeast, and mammalian in vitro assays, and an in vivo micronucleus study in mice.

The pharmacological activity of mifepristone disrupts the estrus cycle of adult rats at a dose of 0.3 mg/kg (less than human exposure at the maximum clinical dose, based on body surface area). However, following withdrawal of treatment and subsequent resumption of the estrus cycle, there was no effect on reproductive function when mated.

A single subcutaneous dose of mifepristone (up to 100 mg/kg) to rats on the first day after birth did not adversely affect future reproductive function in males or females, although the onset of puberty was slightly premature in dosed females. Repeated doses of mifepristone (1 mg every other day) to neonatal rats resulted in potentially adverse fertility effects, including oviduct and ovary malformations in females, delayed male puberty, deficient male sexual behavior, reduced testicular size, and lowered ejaculation frequency.

14 CLINICAL STUDIES

14.1 Cushing's Syndrome

An uncontrolled, open-label, 24-week, multicenter clinical study was conducted to evaluate the safety and efficacy of Korlym in the treatment of endogenous Cushing's syndrome. The study enrolled 50 subjects with clinical and biochemical evidence of hypercortisolemia despite prior surgical treatment and radiotherapy. The reasons for medical treatment were failed surgery, recurrence of disease, and poor medical candidate for surgery. Forty-three patients (86%) had Cushing's disease, four patients (8%) had ectopic ACTH secretion, and three (6%) had adrenal carcinoma. Baseline characteristics included: mean age of 45 years (range 26 to 71), mean BMI of 36 kg/m^2 (range 24 to 66), mean weight 100 kg (range 61 to 199), and mean waist circumference was 119 cm (range 89 to 178); 70% were female; 84% were white and 16% were black or African American. Baseline mean urinary free cortisol level was 365 µg per 24 hr.

Patients belonged to one of two cohorts: a "diabetes" cohort (29 patients, 26 with type 2 diabetes and 3 with glucose intolerance), and a "hypertension" cohort (21 patients). Efficacy was evaluated separately in the two cohorts. Korlym treatment was started in all patients at a dose of 300 mg once a day. The study protocol allowed an increase in dose to 600 mg after 2 weeks, and then by additional 300 mg increments

every 4 weeks to a maximum of 900 mg per day for patients <60 kg, or 1200 mg per day for patients >60 kg, based on clinical tolerance and clinical response.

Results in the diabetes cohort

Patients in the diabetes cohort underwent standard oral glucose tolerance tests at baseline and periodically during the clinical study. Anti-diabetic medications were allowed but had to be kept stable during the trial and patients had to be on stable anti-diabetic regimens prior to enrollment. The primary efficacy analysis for the diabetes cohort was an analysis of responders. A responder was defined as a patient who had a ≥ 25% reduction from baseline in glucose AUC. The primary efficacy analysis was conducted in the modified intent-to-treat- population (n=25) defined as all patients who received a minimum of 30 days on Korlym. Fifteen of 25 patients (60%) were treatment responders (95% CI: 39%,78%).

Mean HbA1C was 7.4% in the 24 patients with HbA1c values at baseline and Week 24. For these 24 patients mean reduction in HbA1c was 1.1% (95% CI -1.6, -0.7) from baseline to the end of the trial. Fourteen of 24 patients had above normal HbA1c levels at baseline, ranging between 6.7% and 10.4%; all of these patients had reductions in HbA1c by the end of the study (range -0.4 to -4.4%) and eight of 14 patients (57%) normalized HbA1c levels at trial end. Antidiabetic medications were reduced in 7 of the 15 DM subjects taking antidiabetic medication and remained constant in the others.

Results in the hypertension cohort

There were no changes in mean systolic and diastolic blood pressures at the end of the trial relative to baseline in the modified intent-to-treat population (n=21).

Signs and symptoms of Cushing's syndrome in both cohorts

Individual patients showed varying degrees of improvement in Cushing's syndrome manifestations such as cushingoid appearance, acne, hirsutism, striae, psychiatric symptoms, and excess total body weight. Because of the variability in clinical presentation and variability of response in this open label trial, it is uncertain whether these changes could be ascribed to the effects of Korlym.

16 HOW SUPPLIED/STORAGE AND HANDLING

Korlym is supplied as a light yellow to yellow, film-coated, oval-shaped tablet debossed with "Corcept" on one side and "300" on the other. Each tablet contains 300 mg of mifepristone. Korlym tablets are available in bottles of 28 tablets (NDC 76346-073-01) and bottles of 280 tablets (NDC 76346-073-02).

Store at controlled room temperature, 25 °C (77 °F); excursions permitted to 15 to 30 ° C (59 – 86 °F). *[See USP Controlled Room Temperature]*

17 PATIENT COUNSELING INFORMATION

As a part of patient counseling, doctors must review the Korlym Medication Guide with every patient. *[See FDA-Approved Medication Guide (17.3)]*

17.1 Importance of Preventing Pregnancy

- Advise patients that Korlym will cause termination of pregnancy. Korlym is contraindicated in pregnant patients.

- Counsel females of reproductive potential regarding pregnancy prevention and planning with a non-hormonal contraceptive prior to use of Korlym and up to one month after the end of treatment.
- Instruct patients to contact their physician immediately if they suspect or confirm they are pregnant.

Medication Guide
Korlym™ (KOR-lim)
(mifepristone)
tablets

Read this Medication Guide before you start taking Korlym and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment.

What is the most important information I should know about Korlym?

Korlym can cause serious side effects, including:

- **Loss of a pregnancy.** Women who can become pregnant must:
  - have a negative pregnancy test before starting Korlym
  - have a negative pregnancy test before restarting Korlym if you stop taking it for more than 14 days
  - use a non-hormonal form of birth control while taking Korlym and for 1 month after stopping Korlym. Talk to your doctor about how to prevent pregnancy. Tell your doctor right away if you think you may be pregnant.

What is Korlym?

Korlym is a prescription medicine used to treat high blood sugar (hyperglycemia) caused by high cortisol levels in the blood (hypercortisolism) in adults with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or cannot have surgery.

Korlym is not for people who have type 2 diabetes mellitus not caused by Cushing's syndrome.

It is not known if Korlym is safe and effective in children.

Who should not take Korlym?

Do not take Korlym if you:

- **are pregnant.** See "What is the most important information I should know about Korlym?"
- **are taking:**
  - simvastatin (Zocor®, Vytorin®, Juvisync®, Simcor®)
  - lovastatin (Mevacor®, Altoprev®, Advicor®)
  - cyclosporine (Gengraf®, Neoral®, Restais®, Sandimmune®)
  - dihydroergotamine (Migranal®)
  - ergotamine (Ergomar®, Migerot®)
  - fentanyl (Abstral®, Actiq®, Duragesic®, Fentora®, Lazanda®, Onsolis®, Sublimaze Preservative Free®, Sunsys®)
  - pimozide (Orap®)

- quinidine (Neudexta®)
- sirolimum (Rapamune®, Torisel®)
- tacrolimus (Prograf®, Protopic®)

- must take corticosteroid medicines for other serious medical problems
- are a woman who still has her uterus (womb) **and** have:
  - unexplained bleeding from your vagina
  - changes in the cells lining your uterus (endometrial hyperplasia) or cancer of the lining of your uterus (endometrial cancer)
- are allergic to mifepristone or any of the ingredients in Korlym. See the end of this Medication Guide for a complete list of ingredients in Korlym.

Talk to your doctor before taking Korlym if you have any of these conditions.

What should I tell my doctor before taking Korlym?
Before taking Korlym, tell your doctor if you:

- have low potassium in your blood (hypokalemia)
- have or have had a bleeding problem or are taking medicines to thin your blood
- have or have had heart problems
- have had an organ transplant
- have been taking medicines called corticosteroids (cortisone, dexamethasone, methylprednisolone, prednisolone, prednisone)
- are breastfeeding or plan to breastfeed. Korlym passes into your breast milk and may harm your baby. You and your doctor should decide if you will take Korlym or breastfeed. You should not do both.

Tell your doctor about all of the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements.

Using Korlym with certain other medicines can affect each other. Using Korlym with other medicines can cause serious side effects.

Especially tell your doctor if you take:

- medicines to treat:
  - fungal infections (such as ketoconazole)
  - depression
  - HIV infection
  - Hepatitis C infection
  - certain bacterial infections
- steroid medicines such as prednisone
- thyroid hormones

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them to show to your doctor and pharmacist.

How should I take Korlym?

- Take Korlym exactly as your doctor tells you.
- Your doctor may change your dose if needed.
- Korlym is usually taken 1 time each day.
- Take Korlym with food.
- Swallow Korlym whole. **Do not** split, crush or chew Korlym tablets. If you cannot swallow Korlym tablets whole, tell your doctor.

What should I avoid while taking Korlym?

You should not drink grapefruit juice while you take Korlym. Grapefruit juice may increase the amount of Korlym in your blood and increase your chance of having side effects.

What are the possible side effects of Korlym?

Korlym can cause serious side effects including:

- **See "What is the most important information I should know about Korlym?"**
- **reduced effects of adrenal hormones (adrenal insufficiency)**. Korlym stops an adrenal hormone in your body called cortisol from working. Tell your doctor right away if you have any symptoms of adrenal insufficiency. Symptoms may include:
    - unusual tiredness or weakness
    - nausea
    - fatigue
    - low blood pressure (hypotension)
    - low blood sugar (hypoglycemia)
- **low blood potassium (hypokalemia)**. Your doctor should check the level of potassium in your blood before you start taking Korlym and while you take it. Tell your doctor if you have any signs of low potassium. Signs may include:
    - muscle weakness, aches, or cramps
    - abnormal or irregular heartbeats (palpitations)
- **bleeding from the vagina.** Korlym may cause the lining of your uterus to become thick and may cause your uterus to bleed. Tell your doctor right away about any bleeding from your vagina that is not normal for you.
- **problems with the electrical system of your heart (QT interval prolongation).**
- **worsening of symptoms of other medical problems that are treated with corticosteroids when you take corticosteroids and Korlym at the same time.**

The most common side effects of Korlym include:

- nausea
- fatigue
- headache
- low potassium in your blood
- pain in your arms and legs (arthralgia)
- vomiting
- swelling of your arms and legs (peripheral edema)
- high blood pressure
- dizziness
- decreased appetite
- thickening of the lining of the uterus (endometrial hypertrophy)

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Korlym. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Korlym?

Store Korlym at room temperature, between 68°F to 77°F (20°C to 25°C).

Keep Korlym and all medicines out of the reach of children.

General information about the safe and effective use of Korlym

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

Do not use Korlym for a condition for which it was not prescribed. Do not give Korlym to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about Korlym. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Korlym that is written for healthcare professionals.

For more information, call 1-855-4Korlym (1-855-456-7596) or visit www.korlym.com or www.corcept.com.

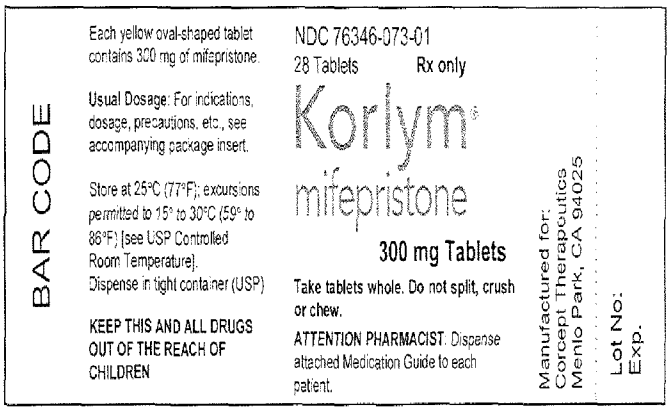
What are the ingredients in Korlym?

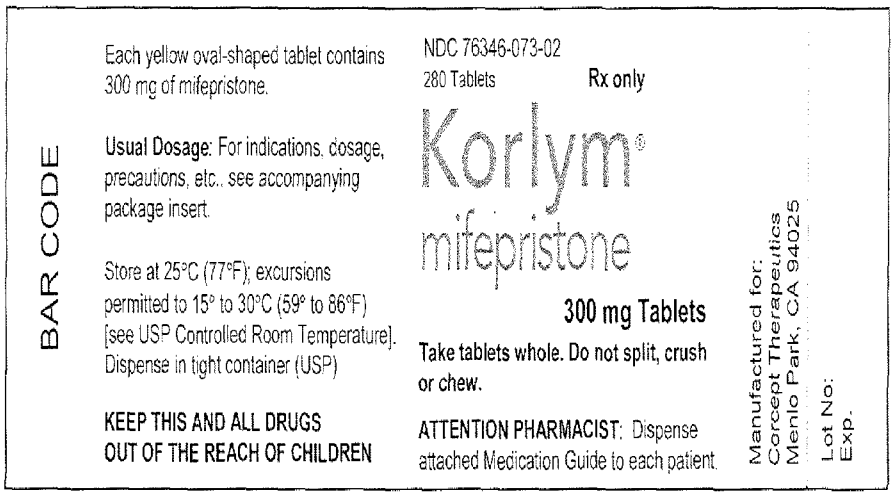
Active ingredient: mifepristone

Inactive ingredients: silicified microcrystalline cellulose, sodium starch glycolate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate, hypromellose, titanium dioxide, triacetin, D&C yellow 10 aluminum lake, polysorbate 80, and FD&C yellow 6 aluminum lake.

This Medication Guide has been approved by the US Food and Drug Administration.

Distributed by:
Corcept Therapeutics Incorporated
149 Commonwealth Avenue
Menlo Park, CA 94025
Issued: 02/2012


BAR CODE
Each yellow oval-shaped tablet contains 300 mg of mifepristone.
Usual Dosage: For indications, dosage, precautions, etc., see accompanying package insert.
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].
Dispense in tight container (USP)
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN
NDC 76346-073-01
28 Tablets Rx only
Korlym®
mifepristone
300 mg Tablets
Take tablets whole. Do not split, crush or chew.
ATTENTION PHARMACIST: Dispense attached Medication Guide to each patient.
Manufactured for:
Corcept Therapeutics
Menlo Park, CA 94025
Lot No:
Exp.


BAR CODE
Each yellow oval-shaped tablet contains 300 mg of mifepristone.
Usual Dosage: For indications, dosage, precautions, etc., see accompanying package insert.
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in tight container (USP)
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN
NDC 76346-073-02
280 Tablets
Rx only
Korlym®
mifepristone
300 mg Tablets
Take tablets whole. Do not split, crush or chew.
ATTENTION PHARMACIST: Dispense attached Medication Guide to each patient.
Manufactured for:
Corcept Therapeutics
Menlo Park, CA 94025
Lot No:
Exp.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
02/17/2012

EXHIBIT 4

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202107

NDA APPROVAL

Corcept Therapeutics
Attention: Luana Staiger
Regulatory Affairs
149 Commonwealth Drive
Menlo Park, CA 94025

Dear Ms. Staiger:

Please refer to your New Drug Application (NDA) dated April 15, 2011, received April 18, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Korlym (mifepristone) tablets, 300 mg.

We acknowledge receipt of your amendments dated April 19, 22, and 25, June 9 and 30, July 11, 12, 13 (2), 20, and 27, August 4 (2) and 12, September 21 (2), October 4, 17, and 19, November 10, 18, and 21, and December 7 and 14, 2011, January 19 and 23, and February 6, 9, and 15, 2012. We also acknowledge receipt of your e-mails dated February 17, 2012, which includes the agreed-upon labeling.

This new drug application provides for the use of Korlym (mifepristone) for the control of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.

We have completed our review of this application, as amended. It is **approved**, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide).

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CONTAINER LABELS

We acknowledge your February 12, 2012, submission containing final printed container labels.

Submit final printed container labels that are identical to the enclosed container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 202107**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of endometrial hyperplasia and retinopathy associated with long-term exposure to Korlym (mifepristone) therapy, and to assess a signal of a serious risk of major adverse cardiovascular events due to reductions in HDL-cholesterol associated with the use of Korlym (mifepristone).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1875-1 A drug utilization study to better characterize the reporting rates of adverse events associated with the long-term use of Korlym (mifepristone). These data will provide a denominator for the adverse events of special interest (endometrial hyperplasia and/or vaginal bleeding, retinopathy, and major adverse cardiovascular events) reported through enhanced pharmacovigilance and associated with long-term exposure to Korlym (mifepristone) therapy.

The timetable you submitted on February 12, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2012
Interim Report Submissions:	08/2012
	02/2013
	02/2014
	02/2015
	02/2016
Final Report Submission:	02/2017

Finally, increased exposure to mifepristone is associated with serious risks for severe hypokalemia and adrenal insufficiency. Mifepristone is a CYP3A4 substrate and it is anticipated that co-administration with strong CYP3A4 inhibitors may be necessary. We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to characterize the effect of co-administration of strong CYP3A4 inhibitors on increasing mifepristone drug levels and to assess the potential for the known serious risks of severe hypokalemia and adrenal insufficiency.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1875-2 A drug-drug interaction clinical trial to determine a quantitative estimate of the change in exposure of mifepristone following co-administration of ketoconazole (a strong CYP3A4 inhibitor).

The timetable you submitted on February 12, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	08/2012
Trial Completion:	05/2013
Final Report Submission:	08/2013

Submit the protocols to your IND 076480, with a cross-reference letter to this NDA. Submit all final reports to your NDA.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

We acknowledge receipt of your submission dated April 15, 2011, of a proposed risk evaluation and mitigation strategy (REMS). We have determined that, at this time, a REMS is not necessary for Korlym (mifepristone) to ensure that its benefits outweigh its risks. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form.

For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We request that for a period of 5 years, you submit reports of all cases of endometrial hyperplasia and/or vaginal bleeding, retinopathy, and major adverse cardiovascular events as 15-day alert reports, and that you provide analyses of clinical trial and post-marketing cases of these adverse events of special interest in your periodic safety update reports.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling (package insert and Medication Guide)
Container Labels

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Korlym™ safely and effectively. See full prescribing information for Korlym.

Korlym™ (mifepristone) 300 mg Tablets

Initial U.S Approval 2000

WARNING: TERMINATION OF PREGNANCY

See full prescribing information for complete boxed warning.

Mifepristone has potent antiprogestational effects and will result in the termination of pregnancy. Pregnancy must therefore be excluded before the initiation of treatment with Korlym, or if treatment is interrupted for more than 14 days in females of reproductive potential.

----------**INDICATIONS AND USAGE**----------
Korlym (mifepristone) is a cortisol receptor blocker indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.

Important Limitations of Use (1.1)
- Do not use for the treatment of type 2 diabetes mellitus unrelated to endogenous Cushing's syndrome.

----------**DOSAGE AND ADMINISTRATION**----------
- Administer once daily orally with a meal (2).
- The recommended starting dose is 300 mg once daily (2).
- Renal impairment: do not exceed 600 mg once daily.
- Mild-to-moderate hepatic impairment: do not exceed 600 mg once daily. Do not use in severe hepatic impairment.

Based on clinical response and tolerability, the dose may be increased in 300 mg increments to a maximum of 1200 mg once daily. Do not exceed 20 mg/kg per day (2).

----------**DOSAGE FORMS AND STRENGTHS**----------
• 300 mg tablet

----------**CONTRAINDICATIONS**----------
- Pregnancy (4.1, 8.1)
- Use of simvastatin or lovastatin and CYP 3A substrates with narrow therapeutic range (4.2)
- Concurrent long-term corticosteroid use (4.3)
- Women with history of unexplained vaginal bleeding (4.4)
- Women with endometrial hyperplasia with atypia or endometrial carcinoma (4.4)

----------**WARNINGS AND PRECAUTIONS**----------
- *Adrenal insufficiency*: Patients should be closely monitored for signs and symptoms of adrenal insufficiency (5.1).
- *Hypokalemia*: Hypokalemia should be corrected prior to treatment and monitored for during treatment (5.2).
- *Vaginal bleeding and endometrial changes*: Women may experience endometrial thickening or unexpected vaginal bleeding. Use with caution if patient also has a hemorrhagic disorder or is on anti-coagulant therapy (5.3).
- *QT interval prolongation*: Avoid use with QT interval-prolonging drugs, or in patients with potassium channel variants resulting in a long QT interval (5.4).
- *Use of Strong CYP3A Inhibitors:* Concomitant use can increase mifepristone plasma levels significantly. Use only when necessary and limit mifepristone dose to 300 mg (5.6).

----------**ADVERSE REACTIONS**----------
Most common adverse reactions in Cushing's syndrome (≥ 20%): nausea, fatigue, headache, decreased blood potassium, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite, endometrial hypertrophy

To report suspected adverse reactions, contact Corcept Therapeutics at 1-855-844-3270 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------**DRUG INTERACTIONS**----------
• Drugs metabolized by CYP3A: Administer drugs that are metabolized by CYP3A at the lowest dose when used with Korlym (7.1).
• CYP3A inhibitors: Caution should be used when Korlym is used with strong CYP3A inhibitors. Limit mifepristone dose to 300 mg per day when used with strong CYP3A inhibitors (5.6, 7.2).
• CYP3A inducers: Do not use Korlym with CYP3A inducers (7.3).
• Drugs metabolized by CYP2C8/2C9: Use the lowest dose of CYP2C8/2C9 substrates when used with Korlym (7.4).
• Drugs metabolized by CYP2B6: Use of Korlym should be done with caution with bupropion and efavirenz (7.5).
• Hormonal contraceptives: Do not use with Korlym (7.6).

----------**USE IN SPECIFIC POPULATIONS**----------
- Nursing mothers: Discontinue drug or discontinue nursing (8.3).

See Section 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide

FULL PRESCRIBING INFORMATION: Contents*

*Sections or subsections omitted from the full prescribing information are not listed

Korlym™ (mifepristone) 300 mg tablets for oral use

FULL PRESCRIBING INFORMATION

WARNING: TERMINATION OF PREGNANCY

Mifepristone is a potent antagonist of progesterone and cortisol via the progesterone and glucocorticoid (GR-II) receptors, respectively. The antiprogestational effects will result in the termination of pregnancy. Pregnancy must therefore be excluded before the initiation of treatment with Korlym and prevented during treatment and for one month after stopping treatment by the use of a non-hormonal medically acceptable method of contraception unless the patient has had a surgical sterilization, in which case no additional contraception is needed. Pregnancy must also be excluded if treatment is interrupted for more than 14 days in females of reproductive potential.

1 INDICATIONS AND USAGE

Korlym (mifepristone) is a cortisol receptor blocker indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.

LIMITATIONS OF USE:

- Korlym should not be used in the treatment of patients with type 2 diabetes unless it is secondary to Cushing's syndrome.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosage

The recommended starting dose is 300 mg orally once daily. Korlym must be given as a single daily dose. Korlym should always be taken with a meal. Patients should swallow the tablet whole. Do not split, crush, or chew tablets.

Dosing and titration

The daily dose of Korlym may be increased in 300 mg increments. The dose of Korlym may be increased to a maximum of 1200 mg once daily but should not exceed 20 mg/kg per day. Increases in dose should not occur more frequently than once every 2-4 weeks. Decisions about dose increases should be based on a clinical assessment of tolerability and degree of improvement in Cushing's syndrome manifestations. Changes in glucose control, anti-diabetic medication requirements, insulin levels, and psychiatric symptoms may provide an early assessment of response (within 6 weeks) and may help guide early dose titration. Improvements in cushingoid appearance, acne, hirsutism, striae, and body weight occur over a longer period of time and, along with measures of glucose control, may be used to determine dose changes beyond the first 2 months of therapy. Careful and gradual titration of Korlym accompanied by monitoring for recognized adverse reactions (*See Warnings and Precautions 5.1 and 5.2*) may reduce the risk of severe adverse reactions. Dose reduction or even dose discontinuation may be needed in some

clinical situations. If Korlym treatment is interrupted, it should be reinitiated at the lowest dose (300 mg). If treatment was interrupted because of adverse reactions, the titration should aim for a dose lower than the one that resulted in treatment interruption.

2.2 Dosing in Renal Impairment

No change in initial dose of Korlym is required in renal impairment. The maximum dose should be limited to 600 mg. *[See Renal Impairment (8.6) and Clinical Pharmacology (12.3)]*

2.3 Dosing in Hepatic Impairment

No change in the initial dose of Korlym is required in mild to moderate hepatic impairment. The maximum dose should be limited to 600 mg. Korlym should not be used in severe hepatic impairment. *[See Hepatic Impairment (8.7) and Clinical Pharmacology (12.3)]*

3 DOSAGE FORMS AND STRENGTHS

Korlym is supplied as a light yellow to yellow oval-shaped tablet debossed with "Corcept" on one side and "300" on the other. Each tablet contains 300 mg of mifepristone. The tablets are not scored.

4 CONTRAINDICATIONS

4.1 Pregnancy

Korlym is contraindicated in women who are pregnant. Pregnancy must be excluded before the initiation of treatment with Korlym or if treatment is interrupted for more than 14 days in females of reproductive potential. Nonhormonal contraceptives should be used during and one month after stopping treatment in all women of reproductive potential. *[See Use in Specific Populations 8.8]*

4.2 Drugs Metabolized by CYP3A

Korlym is contraindicated in patients taking simvastatin, lovastatin, and CYP3A substrates with narrow therapeutic ranges, such as cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, due to an increased risk of adverse events. *[See Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*

4.3 Corticosteroid Therapy Required for Lifesaving Purposes

Korlym is contraindicated in patients who require concomitant treatment with systemic corticosteroids for serious medical conditions or illnesses (e.g., immunosuppression after organ transplantation) because Korlym antagonizes the effect of glucocorticoids.

4.4 Women with Risk of Vaginal Bleeding or Endometrial Changes

Korlym is contraindicated in the following:

- Women with a history of unexplained vaginal bleeding
- Women with endometrial hyperplasia with atypia or endometrial carcinoma

4.5 Known Hypersensitivity to Mifepristone

Korlym is contraindicated in patients with prior hypersensitivity reactions to mifepristone or to any of the product components.

5 WARNINGS AND PRECAUTIONS

5.1 Adrenal Insufficiency

Patients receiving mifepristone may experience adrenal insufficiency. Because serum cortisol levels remain elevated and may even increase during treatment with Korlym, serum cortisol levels do not provide an accurate assessment of hypoadrenalism in patients receiving Korlym. Patients should be closely monitored for signs and symptoms of adrenal insufficiency, including weakness, nausea, increased fatigue, hypotension, and hypoglycemia. If adrenal insufficiency is suspected, discontinue treatment with Korlym immediately and administer glucocorticoids without delay. High doses of supplemental glucocorticoids may be needed to overcome the glucocorticoid receptor blockade produced by mifepristone. Factors considered in deciding on the duration of glucocorticoid treatment should include the long half-life of mifepristone (85 hours).

Treatment with Korlym at a lower dose can be resumed after resolution of adrenal insufficiency. Patients should also be evaluated for precipitating causes of hypoadrenalism (infection, trauma, etc.).

5.2 Hypokalemia

In a study of patients with Cushing's syndrome, hypokalemia was observed in 44% of subjects during treatment with Korlym. Hypokalemia should be corrected prior to initiating Korlym. During Korlym administration, serum potassium should be measured 1 to 2 weeks after starting or increasing the dose of Korlym and periodically thereafter. Hypokalemia can occur at any time during Korlym treatment. Mifepristone-induced hypokalemia should be treated with intravenous or oral potassium supplementation based on event severity. If hypokalemia persists in spite of potassium supplementation, consider adding mineralocorticoid antagonists.

5.3 Vaginal Bleeding and Endometrial Changes

Being an antagonist of the progesterone receptor, mifepristone promotes unopposed endometrial proliferation that may result in endometrium thickening, cystic dilatation of endometrial glands, and vaginal bleeding. Korlym should be used with caution in women who have hemorrhagic disorders or are receiving concurrent anticoagulant therapy. Women who experience vaginal bleeding during Korlym treatment should be referred to a gynecologist for further evaluation.

5.4 QT Interval Prolongation

Mifepristone and its metabolites block IKr. Korlym prolongs the QTc interval in a dose-related manner. There is little or no experience with high exposure, concomitant dosing with other QT-prolonging drugs, or potassium channel variants resulting in a long QT interval. *[See Warnings & Precautions (5.6)]* To minimize risk, the lowest effective dose should always be used.

5.5 Exacerbation/Deterioration of Conditions Treated with Corticosteroids

Use of Korlym in patients who receive corticosteroids for other conditions (e.g., autoimmune disorders) may lead to exacerbation or deterioration of such conditions, as Korlym antagonizes the desired effects of glucocorticoid in these clinical settings. For medical conditions in which chronic corticosteroid therapy is life-saving (e.g., immunosuppression in organ transplantation), Korlym is contraindicated. *[See Contraindications (4.3)]*

5.6 Use of Strong CYP3A Inhibitors

Korlym should be used with extreme caution in patients taking ketoconazole and other strong inhibitors of CYP3A, such as itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, nefazodone, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, or voriconazole, as these could substantially increase the concentration of mifepristone in the blood. The benefit of concomitant use of these agents should be carefully weighed against the potential risks. Mifepristone should be used in combination with strong CYP3A inhibitors only when necessary, and in such cases the dose should be limited to 300 mg per day. *[See Warnings & Precautions (5.4), Drug Interactions (7.2), and Clinical Pharmacology (12.3)]*

5.7 *Pneumocystis jiroveci* Infection

Patients with endogenous Cushing's syndrome are at risk for opportunistic infections such as *Pneumocystis jiroveci* pneumonia during Korlym treatment. Patients may present with respiratory distress shortly after initiation of Korlym. Appropriate diagnostic tests should be undertaken and treatment for *Pneumocystis jiroveci* should be considered.

5.8 Potential Effects of Hypercortisolemia

Korlym does not reduce serum cortisol levels. Elevated cortisol levels may activate mineralcorticoid receptors which are also expressed in cardiac tissues. Caution should be used in patients with underlying heart conditions including heart failure and coronary vascular disease.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

Safety data on the use of Korlym are available from 50 patients with Cushing's syndrome enrolled in an uncontrolled, open-label, multi-center trial (Study 400). Forty-three patients had Cushing's disease and all except one had previously undergone pituitary surgery. Four patients had ectopic ACTH secretion, and three had adrenal carcinoma. Patients were treated for up to 24 weeks. A dose of 300 mg per day was administered for the initial 14 days; thereafter, the dose could be escalated in increments of 300 mg per day based on assessments of tolerability and clinical response. Doses were escalated up to 900 mg per day for patients <60 kg, or 1200 mg per day for patients >60 kg.

The most frequently reported adverse reactions (reported in ≥20% of patients, regardless of relationship to Korlym) were nausea, fatigue, headache, decreased blood potassium, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite, and endometrial hypertrophy. Drug-related adverse events resulted in dose interruption or reduction in study drug in 40% of patients.

The adverse reactions that occurred in ≥10% of the Cushing's syndrome patients receiving Korlym, regardless of relationship to Korlym, are shown in Table 1.

Table 1. Treatment Emergent Adverse Events Occurring in ≥10% of Cushing's Syndrome Patients Receiving Korlym

Body System/Adverse Reaction	Percent (%) of Patients Reporting Event (n = 50)
Gastrointestinal disorders	
Nausea	48
Vomiting	26
Dry mouth	18
Diarrhea	12
Constipation	10
General disorders and administration/site conditions	
Fatigue	48
Edema peripheral	26
Pain	14
Nervous system disorders	
Headache	44
Dizziness	22
Somnolence	10
Musculoskeletal and connective tissue disorders	
Arthralgia	30
Back pain	16
Myalgia	14
Pain in extremity	12
Investigations	
Blood potassium decreased	34
Thyroid function test abnormal	18
Infections and infestations	
Sinusitis	14
Nasopharyngitis	12
Metabolism and nutrition disorders	
Decreased appetite	20
Anorexia	10
Vascular disorders	
Hypertension	24
Reproductive system and breast disorders	
Endometrial hypertrophy	38*
Respiratory, thoracic, and mediastinal disorders	
Dyspnea	16
Psychiatric disorders	
Anxiety	10

*The denominator was 26 females who had baseline and end-of-trial transvaginal ultrasound

6.2 Laboratory Tests

Reductions in high density lipoprotein-cholesterol (HDL-C) levels have been observed following treatment with Korlym. In study subjects that experienced declines in HDL-C, levels returned to baseline following discontinuation of drug. The clinical significance of the treatment-related reduction in HDL-C levels in patients with Cushing's syndrome is not known.

In a study of patients with Cushing's syndrome, hypokalemia was observed in 44% of subjects during treatment with Korlym. In these cases, hypokalemia responded to treatment with potassium supplementation and/or mineralocorticoid antagonist therapy (e.g., spironolactone or eplerenone). Hypokalemia should be corrected prior to initiating Korlym. *[See Warnings and Precautions (5.2)]*

Elevations of thyroid-stimulating hormone (TSH) were seen in subjects treated with Korlym. Of the 42 subjects with detectable TSH at baseline, eight (19%) had increases in TSH above the normal range, while remaining asymptomatic. The TSH levels returned to normal in most patients without intervention when Korlym was discontinued at the end of the study.

6.3 Vaginal Bleeding and Endometrial Changes

In Study 400, the thickness of the endometrium increased from a mean of 6.14 mm at baseline (n=23) to 15.7 mm at end-of-trial (n=18) in premenopausal women; in postmenopausal women the increase was from 2.75 mm (n=6) to 7.35 mm (n=8). Endometrial thickness above the upper limit of normal was reported in 10/26 females who had baseline and end-of-trial transvaginal ultrasound (38%). The endometrial thickness returned to the normal range in 3 out of 10 patients 6 weeks after treatment cessation at the end of the study. Vaginal bleeding occurred in 5 out of 35 females (14%). Two of five subjects with vaginal bleeding had normal endometrial thickness. Endometrial biopsies were performed in six patients; five of these patients had endometrial thickening. No endometrial carcinoma was detected in the sampled cases.

6.4 Additional Data from Clinical Trials

The following are adverse events that were reported in Study 400 at frequencies of $\geq$ 5% to 10%, and may be related to Korlym's mechanism of action:

Gastrointestinal disorders: gastroesophageal reflux, abdominal pain

General disorders and administration site conditions: asthenia, malaise, edema, pitting edema, thirst

Investigations: blood triglycerides increased

Metabolism and nutrition disorders: hypoglycemia

Musculoskeletal and connective tissue disorders: muscular weakness, flank pain, musculoskeletal chest pain

Psychiatric disorders: insomnia

Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia *[See Warnings and Precautions (5.3)]*

6.4.1 Adrenal Insufficiency

Adrenal insufficiency was reported in two subjects (4%) in Study 400. The most typical symptoms of adrenal insufficiency were nausea and decreased appetite. No hypotension or hypoglycemia was reported

during the events. Adrenal insufficiency resolved in both cases with Korlym interruption and /or dexamethasone administration.

6.4.2 Rash

Generalized, maculo-papular rash was reported in 2 subjects (4%) in Study 400. Two additional subjects developed pruritus (4%). None resulted in discontinuation of Korlym, and all the events resolved by the end of the study.

7 DRUG INTERACTIONS

Based on the long terminal half-life of mifepristone after reaching steady state, at least 2 weeks should elapse after cessation of Korlym before initiating or increasing the dose of any interacting concomitant medication.

7.1 Drugs Metabolized by CYP3A

Because Korlym is an inhibitor of CYP3A, concurrent use of Korlym with a drug whose metabolism is largely or solely mediated by CYP3A is likely to result in increased plasma concentrations of the drug. Discontinuation or dose reduction of such medications may be necessary with Korlym co-administration.

Korlym increased the exposure to simvastatin and simvastatin acid significantly in healthy subjects. Concomitant use of simvastatin or lovastatin is contraindicated because of the increased risk of myopathy and rhabdomyolysis. *[See Contraindications (4.2), Clinical Pharmacology 12.3]*

The exposure of other substrates of CYP3A with narrow therapeutic ranges, such as cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, may be increased by concomitant administration with Korlym. Therefore, the concomitant use of such CYP3A substrates with Korlym is contraindicated. *[See Contraindications (4.2)]*

Other drugs with similar high first pass metabolism in which CYP3A is the primary route of metabolism should be used with extreme caution if co-administered with Korlym. The lowest possible dose and/or a decreased frequency of dosing must be used with therapeutic drug monitoring when possible. Use of alternative drugs without these metabolic characteristics is advised when possible with concomitant Korlym.

If drugs that undergo low first pass metabolism by CYP3A or drugs in which CYP3A is not the major metabolic route are co-administered with Korlym, use the lowest dose of concomitant medication necessary, with appropriate monitoring and follow-up. *[See Clinical Pharmacology (12.3)]*

7.2 CYP3A Inhibitors

Medications that inhibit CYP3A could increase plasma mifepristone concentrations and dose reduction of Korlym may be required.

Ketoconazole and other strong inhibitors of CYP3A, such as itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir and fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, mibefradil, nefazodone, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, or voriconazole may increase exposure to mifepristone significantly. The clinical impact of this interaction has not been studied. Therefore, extreme caution should be used when these drugs are prescribed in

combination with Korlym. The benefit of concomitant use of these agents should be carefully weighed against the potential risks. The dose of Korlym should be limited to 300 mg and used only when necessary. *[See Warnings & Precautions (5.6)]*

Moderate inhibitors of CYP3A, such as amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, or verapamil, should be used with caution when administered in combination with Korlym.

7.3 CYP3A Inducers

No medications that induce CYP3A have been studied when co-administered with Korlym. Avoid co-administration of Korlym and CYP3A inducers such as rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine, and St. John's wort.

7.4 Drugs Metabolized by CYP2C8/2C9

Because Korlym is an inhibitor of CYP2C8/2C9, concurrent use of Korlym with a drug whose metabolism is largely or solely mediated by CYP2C8/2C9 is likely to result in increased plasma concentrations of the drug.

Korlym significantly increased exposure of fluvastatin, a typical CYP2C8/2C9 substrate, in healthy subjects. When given concomitantly with Korlym, drugs that are substrates of CYP2C8/2C9 (including non-steroidal anti-inflammatory drugs, warfarin, and repaglinide) should be used at the smallest recommended doses, and patients should be closely monitored for adverse effects. *[See Clinical Pharmacology (12.3)]*

7.5 Drugs Metabolized by CYP2B6

Mifepristone is an inhibitor of CYP2B6 and may cause significant increases in exposure of drugs that are metabolized by CYP2B6 such as bupropion and efavirenz. Since no study has been conducted to evaluate the effect of mifepristone on substrates of CYP2B6, the concomitant use of bupropion and efavirenz should be undertaken with caution. *[See Clinical Pharmacology (12.3)]*

7.6 Use of Hormonal Contraceptives

Mifepristone is a progesterone-receptor antagonist and will interfere with the effectiveness of hormonal contraceptives. Therefore, non-hormonal contraceptive methods should be used.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Category X

Korlym is contraindicated in pregnancy. Korlym can cause fetal harm when administered to a pregnant woman because the use of Korlym results in pregnancy loss. The inhibition of both endogenous and exogenous progesterone by mifepristone at the progesterone receptor results in pregnancy loss. If Korlym is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. *[See Contraindications (4.1)]*

Human Data

In a report of thirteen live births after single dose mifepristone exposure, no fetal abnormalities were noted.

Animal Data

Teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than human exposure at the maximum clinical dose, based on body surface area) were carried out. Because of the anti-progestational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at less than human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from antagonism of the progesterone receptor.

8.3 Nursing Mothers

Mifepristone is present in human milk of women taking the drug. Because of the potential for serious adverse reactions in nursing infants from Korlym, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of Korlym in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies with Korlym did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger people.

8.6 Renal Impairment

The maximum dose should not exceed 600 mg per day in renally impaired patients. *[See Clinical Pharmacology (12.3)]*

8.7 Hepatic Impairment

In patients with mild to moderate hepatic impairment, the maximum dose should not exceed 600 mg per day. The pharmacokinetics of mifepristone in patients with severe hepatic impairment has not been studied, and Korlym should not be used in these patients. *[See Clinical Pharmacology (12.3)]*

8.8 Females of Reproductive Potential

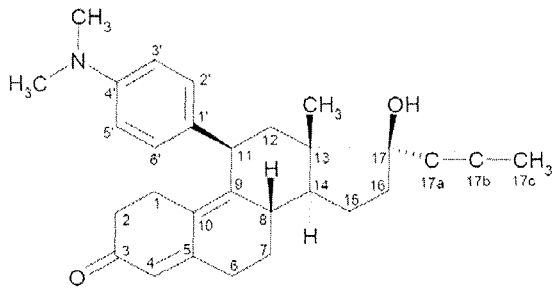
Due to its anti-progestational activity, Korlym causes pregnancy loss. Exclude pregnancy before the initiation of treatment with Korlym or if treatment is interrupted for more than 14 days in females of reproductive potential. Recommend contraception for the duration of treatment and for one month after stopping treatment using a non-hormonal medically acceptable method of contraception. If the patient has had surgical sterilization, no additional contraception is needed.

10 OVERDOSAGE

There is no experience with overdosage of Korlym.

11 DESCRIPTION

Korlym (mifepristone) is a cortisol receptor blocker for oral administration. The chemical name of mifepristone is 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(1-propynyl)-estra-4, 9-dien-3-one. The chemical formula is $C_{29}H_{35}NO_2$; the molecular weight is 429.60; and the structural formula is:



Mifepristone demonstrates a pH-related solubility profile. The greatest solubility is achieved in acidic media (~ 25 mg/mL at pH 1.5) and solubility declines rapidly as the pH is increased. At pH values above 2.5 the solubility of mifepristone is less than 1 mg/mL.

Each Korlym tablet for oral use contains 300 mg of mifepristone. The inactive ingredients of Korlym tablets are silicified microcrystalline cellulose, sodium starch glycolate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate, hypromellose, titanium dioxide, triacetin, D&C yellow 10 aluminum lake, polysorbate 80, and FD&C yellow 6 aluminum lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mifepristone is a selective antagonist of the progesterone receptor at low doses and blocks the glucocorticoid receptor (GR-II) at higher doses. Mifepristone has high affinity for the GR-II receptor but little affinity for the GR-I (MR, mineralocorticoid) receptor. In addition, mifepristone appears to have little or no affinity for estrogen, muscarinic, histaminic, or monoamine receptors.

12.2 Pharmacodynamics

Because mifepristone acts at the receptor level to block the effects of cortisol, its antagonistic actions affect the hypothalamic-pituitary-adrenal (HPA) axis in such a way as to further increase circulating cortisol levels while, at the same time, blocking their effects.

Mifepristone and the three active metabolites have greater affinity for the glucocorticoid receptor (100%, 61%, 48%, and 45%, respectively) than either dexamethasone (23%) or cortisol (9%).

12.3 Pharmacokinetics

Absorption

Following oral administration, time to peak plasma concentrations of mifepristone occurred between 1 and 2 hours following single dose, and between 1 and 4 hours following multiple doses of 600 mg of

Korlym in healthy volunteers. Mean plasma concentrations of three active metabolites of mifepristone peak between 2 and 8 hours after multiple doses of 600 mg/day, and the combined concentrations of the metabolites exceed that of the parent mifepristone. Exposure to mifepristone is substantially less than dose proportional. Time to steady state is within 2 weeks, and the mean (SD) half-life of the parent mifepristone was 85 (61) hours following multiple doses of 600 mg/day of Korlym.

Studies evaluating the effects of food on the pharmacokinetics of Korlym demonstrate a significant increase in plasma levels of mifepristone when dosed with food. To achieve consistent plasma drug concentrations, patients should be instructed to always take their medication with meals.

Distribution

Mifepristone is highly bound to alpha-1-acid glycoprotein (AAG) and approaches saturation at doses of 100 mg (2.5 μM) or more. Mifepristone and its metabolites also bind to albumin and are distributed to other tissues, including the central nervous system (CNS). As determined in vitro by equilibrium dialysis, binding of mifepristone and its three active metabolites to human plasma proteins was concentration-dependent. Binding was approximately 99.2% for mifepristone, and ranged from 96.1 to 98.9% for the three active metabolites at clinically relevant concentrations.

Metabolism

Cytochrome P450 3A4 (CYP3A4) has been shown to be involved in mifepristone metabolism in human liver microsomes. Two of the known active metabolites are the product of demethylation (one monodemethylated and one di-demethylated), while a third active metabolite results from hydroxylation (monohydroxylated).

Elimination and Excretion

Excretion is primarily (approximately 90%) via the fecal route.

Specific Populations

Renal Impairment

The pharmacokinetics of mifepristone in subjects with severe renal impairment (creatinine clearance [CrCL] < 30 mL/min, but not on dialysis) was evaluated following multiple doses of 1200 mg Korlym for 7 days. Mean exposure to mifepristone increased 31%, with similar or smaller increases in metabolite exposure as compared to subjects with normal renal function (CrCL ≥ 90 mL/min). There was large variability in the exposure of mifepristone and its metabolites in subjects with severe renal impairment as compared to subjects with normal renal function (geometric least square mean ratio [CI] for AUC of mifepristone: 1.21 [0.71-2.06]; metabolite 1: 1.43 [0.84-2.44]; metabolite 2: 1.18 [0.64-2.17] and metabolite 3: 1.19 [0.71-1.99]). No change in the initial dose of Korlym is needed for renal impairment; the maximum dose should not exceed 600 mg per day.

Hepatic Impairment

The pharmacokinetics of mifepristone in subjects with moderate hepatic impairment (Child-Pugh Class B) was evaluated in a single- and multiple-dose study (600 mg for 7 days). The pharmacokinetics in subjects with moderate hepatic impairment was similar to those with normal hepatic function. There was large variability in the exposure of mifepristone and its metabolites in subjects with moderate hepatic impairment as compared to subjects with normal hepatic function (geometric least square mean ratio [CI] for AUC of mifepristone: 1.02 [0.59-1.76]; metabolite 1: 0.95 [0.52-1.71]; metabolite 2: 1.37 [0.71-2.62] and metabolite 3: 0.62 [0.33-1.16]). Due to limited information on safety in patients with mild-to-

moderate hepatic impairment, the maximum dose should not exceed 600 mg per day. The pharmacokinetics of mifepristone in patients with severe hepatic disease has not been studied. Korlym is not recommended in patients with severe hepatic disease.

Drug-Drug Interactions

In Vitro Assessment of Drug Interactions

In vitro studies indicate a potential for CYP-mediated drug interactions by mifepristone and/or its metabolites with substrates of CYP2A6, CYP2C8/2C9, CYP2C19, CYP3A4, CYP1A2, CYP2B6, CYP2D6, and CYP2E1. In vitro studies also indicated an interaction potential for drug transport mediated by P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). In vitro studies indicate mifepristone metabolism is mediated by CYP3A, and that mifepristone also inhibits and induces CYP3A.

In Vivo Assessment of Drug Interactions (see Table 2)

Table 2. Summary Table of Korlym Drug-Drug Interaction Effects

Dosing of Mifepristone	Coadministered Drug	Dosing of Coadministered Drug	Geometric Mean Ratio (analyte ratio with/without drug coadministration)		
			Analyte	AUC	Cmax
Effect of Korlym on Coadministered Drug					
Contraindicated with mifepristone *[See Contraindications (4)]*					
1200 mg once daily for 10 days	simvastatin[1]	80 mg single dose	simvastatin acid simvastatin	15.70 10.40	18.20 7.02
Use lowest dose of coadministered drug, based on clinical experience and/or use of therapeutic drug monitoring					
1200 mg once daily for 10 days	alprazolam[2]	1 mg single dose	alprazolam 4-hydroxy-alprazolam	1.80 0.76	0.81 0.39
1200 mg once daily for 7 days	fluvastatin[3]	40 mg single dose	fluvastatin	3.57	1.76
1200 mg once daily for 10 days	digoxin[4]	0.125 mg once daily	digoxin	1.40	1.64
Effect of Coadministered Drug on Korlym					
No dosing adjustment required					
300 mg once daily for 14 days	cimetidine[5]	800 mg once daily	mifepristone	0.85*	0.75

*No effect = 90% CI within range 0.80 – 1.25

[1] Simvastatin 40 mg dose used as reference for the comparison. Result could be representative of other oral drugs with CYP3A metabolism and high first pass effect: cyclosporine, midazolam, triazolam, pimozide, sildenafil, sirolimus, and tacrolimus

[2] Result could be representative of other oral drugs with CYP3A metabolism and low first pass effect. Clinical significance of any interaction will depend on the therapeutic margin of the drug.

[3] Result could be representative of other oral drugs with CYP2C8/C9 metabolism

[4] Plasma digoxin concentration should be measured after 1 to 2 weeks of concomitant use and following usual clinical practice at appropriate intervals thereafter.

[5]Result could be representative of other mild inhibitors of CYP3A

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Mifepristone was evaluated for carcinogenicity potential in rats and mice. Rats were dosed for up to two years at doses of 5, 25, and 125 mg/kg of mifepristone. The high dose was the maximum tolerated dose, but exposure at all doses was below exposure at the maximum clinical dose based on AUC comparison. Female rats had a statistically significant increase in follicular cell adenomas/carcinomas and liver adenomas. It is plausible that these tumors are due to drug-induced enzyme metabolism, a mechanism not considered clinically relevant, but studies confirming this mechanism were not conducted with mifepristone. Mice were also tested for up to 2 years at mifepristone doses up to the maximum tolerated dose of 125 mg/kg, which provided exposure below the maximum clinical dose based on AUC. No drug-related tumors were seen in mice.

Mifepristone was not genotoxic in a battery of bacterial, yeast, and mammalian in vitro assays, and an in vivo micronucleus study in mice.

The pharmacological activity of mifepristone disrupts the estrus cycle of adult rats at a dose of 0.3 mg/kg (less than human exposure at the maximum clinical dose, based on body surface area). However, following withdrawal of treatment and subsequent resumption of the estrus cycle, there was no effect on reproductive function when mated.

A single subcutaneous dose of mifepristone (up to 100 mg/kg) to rats on the first day after birth did not adversely affect future reproductive function in males or females, although the onset of puberty was slightly premature in dosed females. Repeated doses of mifepristone (1 mg every other day) to neonatal rats resulted in potentially adverse fertility effects, including oviduct and ovary malformations in females, delayed male puberty, deficient male sexual behavior, reduced testicular size, and lowered ejaculation frequency.

14 CLINICAL STUDIES

14.1 Cushing's Syndrome

An uncontrolled, open-label, 24-week, multicenter clinical study was conducted to evaluate the safety and efficacy of Korlym in the treatment of endogenous Cushing's syndrome. The study enrolled 50 subjects with clinical and biochemical evidence of hypercortisolemia despite prior surgical treatment and radiotherapy. The reasons for medical treatment were failed surgery, recurrence of disease, and poor medical candidate for surgery. Forty-three patients (86%) had Cushing's disease, four patients (8%) had ectopic ACTH secretion, and three (6%) had adrenal carcinoma. Baseline characteristics included: mean age of 45 years (range 26 to 71), mean BMI of 36 kg/m^2 (range 24 to 66), mean weight 100 kg (range 61 to 199), and mean waist circumference was 119 cm (range 89 to 178); 70% were female; 84% were white and 16% were black or African American. Baseline mean urinary free cortisol level was 365 µg per 24 hr.

Patients belonged to one of two cohorts: a "diabetes" cohort (29 patients, 26 with type 2 diabetes and 3 with glucose intolerance), and a "hypertension" cohort (21 patients). Efficacy was evaluated separately in the two cohorts. Korlym treatment was started in all patients at a dose of 300 mg once a day. The study protocol allowed an increase in dose to 600 mg after 2 weeks, and then by additional 300 mg increments

every 4 weeks to a maximum of 900 mg per day for patients <60 kg, or 1200 mg per day for patients >60 kg, based on clinical tolerance and clinical response.

Results in the diabetes cohort

Patients in the diabetes cohort underwent standard oral glucose tolerance tests at baseline and periodically during the clinical study. Anti-diabetic medications were allowed but had to be kept stable during the trial and patients had to be on stable anti-diabetic regimens prior to enrollment. The primary efficacy analysis for the diabetes cohort was an analysis of responders. A responder was defined as a patient who had a ≥ 25% reduction from baseline in glucose AUC. The primary efficacy analysis was conducted in the modified intent-to-treat- population (n=25) defined as all patients who received a minimum of 30 days on Korlym. Fifteen of 25 patients (60%) were treatment responders (95% CI: 39%,78%).

Mean HbA1C was 7.4% in the 24 patients with HbA1c values at baseline and Week 24. For these 24 patients mean reduction in HbA1c was 1.1% (95% CI -1.6, -0.7) from baseline to the end of the trial. Fourteen of 24 patients had above normal HbA1c levels at baseline, ranging between 6.7% and 10.4%; all of these patients had reductions in HbA1c by the end of the study (range -0.4 to -4.4%) and eight of 14 patients (57%) normalized HbA1c levels at trial end. Antidiabetic medications were reduced in 7 of the 15 DM subjects taking antidiabetic medication and remained constant in the others.

Results in the hypertension cohort

There were no changes in mean systolic and diastolic blood pressures at the end of the trial relative to baseline in the modified intent-to-treat population (n=21).

Signs and symptoms of Cushing's syndrome in both cohorts

Individual patients showed varying degrees of improvement in Cushing's syndrome manifestations such as cushingoid appearance, acne, hirsutism, striae, psychiatric symptoms, and excess total body weight. Because of the variability in clinical presentation and variability of response in this open label trial, it is uncertain whether these changes could be ascribed to the effects of Korlym.

16 HOW SUPPLIED/STORAGE AND HANDLING

Korlym is supplied as a light yellow to yellow, film-coated, oval-shaped tablet debossed with "Corcept" on one side and "300" on the other. Each tablet contains 300 mg of mifepristone. Korlym tablets are available in bottles of 28 tablets (NDC 76346-073-01) and bottles of 280 tablets (NDC 76346-073-02).

Store at controlled room temperature, 25 °C (77 °F); excursions permitted to 15 to 30 ° C (59 – 86 °F). *[See USP Controlled Room Temperature]*

17 PATIENT COUNSELING INFORMATION

As a part of patient counseling, doctors must review the Korlym Medication Guide with every patient. *[See FDA-Approved Medication Guide (17.3)]*

17.1 Importance of Preventing Pregnancy

- Advise patients that Korlym will cause termination of pregnancy. Korlym is contraindicated in pregnant patients.

- Counsel females of reproductive potential regarding pregnancy prevention and planning with a non-hormonal contraceptive prior to use of Korlym and up to one month after the end of treatment.
- Instruct patients to contact their physician immediately if they suspect or confirm they are pregnant.

Medication Guide
Korlym™ (KOR-lim)
(mifepristone)
tablets

Read this Medication Guide before you start taking Korlym and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment.

What is the most important information I should know about Korlym?

Korlym can cause serious side effects, including:

- **Loss of a pregnancy.** Women who can become pregnant must:
  - have a negative pregnancy test before starting Korlym
  - have a negative pregnancy test before restarting Korlym if you stop taking it for more than 14 days
  - use a non-hormonal form of birth control while taking Korlym and for 1 month after stopping Korlym. Talk to your doctor about how to prevent pregnancy. Tell your doctor right away if you think you may be pregnant.

What is Korlym?

Korlym is a prescription medicine used to treat high blood sugar (hyperglycemia) caused by high cortisol levels in the blood (hypercortisolism) in adults with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or cannot have surgery.

Korlym is not for people who have type 2 diabetes mellitus not caused by Cushing's syndrome.

It is not known if Korlym is safe and effective in children.

Who should not take Korlym?

Do not take Korlym if you:

- **are pregnant.** See "What is the most important information I should know about Korlym?"
- **are taking:**
  - simvastatin (Zocor®, Vytorin®, Juvisync®, Simcor®)
  - lovastatin (Mevacor®, Altoprev®, Advicor®)
  - cyclosporine (Gengraf®, Neoral®, Restais®, Sandimmune®)
  - dihydroergotamine (Migranal®)
  - ergotamine (Ergomar®, Migerot®)
  - fentanyl (Abstral®, Actiq®, Duragesic®, Fentora®, Lazanda®, Onsolis®, Sublimaze Preservative Free®, Sunsys®)
  - pimozide (Orap®)

- quinidine (Neudexta®)
- sirolimum (Rapamune®, Torisel®)
- tacrolimus (Prograf®, Protopic®)

- must take corticosteroid medicines for other serious medical problems
- are a woman who still has her uterus (womb) **and** have:
  - unexplained bleeding from your vagina
  - changes in the cells lining your uterus (endometrial hyperplasia) or cancer of the lining of your uterus (endometrial cancer)
- are allergic to mifepristone or any of the ingredients in Korlym. See the end of this Medication Guide for a complete list of ingredients in Korlym.

Talk to your doctor before taking Korlym if you have any of these conditions.

What should I tell my doctor before taking Korlym?
Before taking Korlym, tell your doctor if you:

- have low potassium in your blood (hypokalemia)
- have or have had a bleeding problem or are taking medicines to thin your blood
- have or have had heart problems
- have had an organ transplant
- have been taking medicines called corticosteroids (cortisone, dexamethasone, methylprednisolone, prednisolone, prednisone)
- are breastfeeding or plan to breastfeed. Korlym passes into your breast milk and may harm your baby. You and your doctor should decide if you will take Korlym or breastfeed. You should not do both.

Tell your doctor about all of the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements.

Using Korlym with certain other medicines can affect each other. Using Korlym with other medicines can cause serious side effects.

Especially tell your doctor if you take:

- medicines to treat:
  - fungal infections (such as ketoconazole)
  - depression
  - HIV infection
  - Hepatitis C infection
  - certain bacterial infections
- steroid medicines such as prednisone
- thyroid hormones

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them to show to your doctor and pharmacist.

How should I take Korlym?

- Take Korlym exactly as your doctor tells you.
- Your doctor may change your dose if needed.
- Korlym is usually taken 1 time each day.
- Take Korlym with food.
- Swallow Korlym whole. **Do not** split, crush or chew Korlym tablets. If you cannot swallow Korlym tablets whole, tell your doctor.

What should I avoid while taking Korlym?

You should not drink grapefruit juice while you take Korlym. Grapefruit juice may increase the amount of Korlym in your blood and increase your chance of having side effects.

What are the possible side effects of Korlym?

Korlym can cause serious side effects including:

- **See "What is the most important information I should know about Korlym?"**
- **reduced effects of adrenal hormones (adrenal insufficiency)**. Korlym stops an adrenal hormone in your body called cortisol from working. Tell your doctor right away if you have any symptoms of adrenal insufficiency. Symptoms may include:
    - unusual tiredness or weakness
    - nausea
    - fatigue
    - low blood pressure (hypotension)
    - low blood sugar (hypoglycemia)
- **low blood potassium (hypokalemia)**. Your doctor should check the level of potassium in your blood before you start taking Korlym and while you take it. Tell your doctor if you have any signs of low potassium. Signs may include:
    - muscle weakness, aches, or cramps
    - abnormal or irregular heartbeats (palpitations)
- **bleeding from the vagina.** Korlym may cause the lining of your uterus to become thick and may cause your uterus to bleed. Tell your doctor right away about any bleeding from your vagina that is not normal for you.
- **problems with the electrical system of your heart (QT interval prolongation).**
- **worsening of symptoms of other medical problems that are treated with corticosteroids when you take corticosteroids and Korlym at the same time.**

The most common side effects of Korlym include:

- nausea
- fatigue
- headache
- low potassium in your blood
- pain in your arms and legs (arthralgia)
- vomiting
- swelling of your arms and legs (peripheral edema)
- high blood pressure
- dizziness
- decreased appetite
- thickening of the lining of the uterus (endometrial hypertrophy)

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Korlym. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Korlym?

Store Korlym at room temperature, between 68°F to 77°F (20°C to 25°C).

Keep Korlym and all medicines out of the reach of children.

General information about the safe and effective use of Korlym

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

Do not use Korlym for a condition for which it was not prescribed. Do not give Korlym to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about Korlym. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Korlym that is written for healthcare professionals.

For more information, call 1-855-4Korlym (1-855-456-7596) or visit www.korlym.com or www.corcept.com.

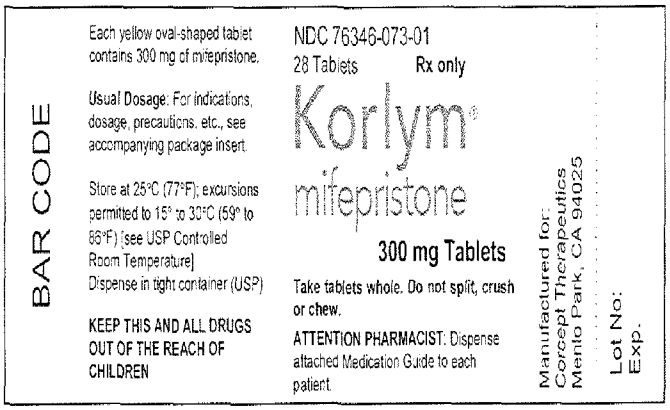
What are the ingredients in Korlym?

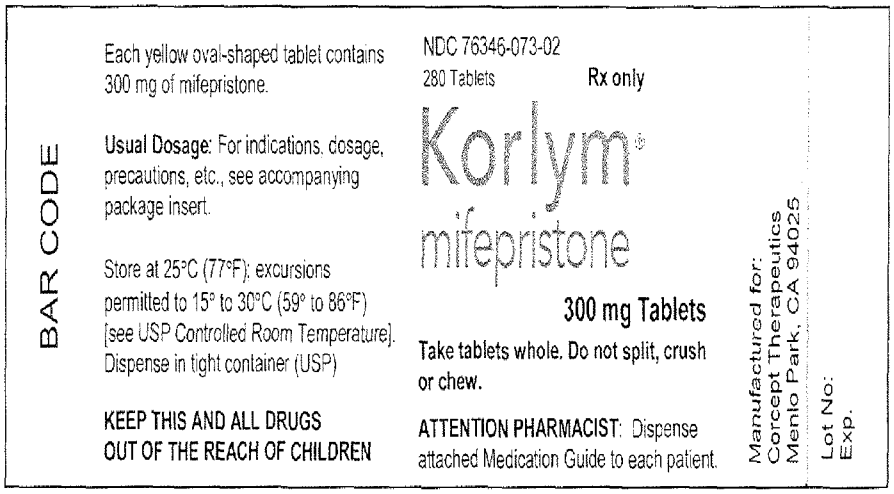
Active ingredient: mifepristone

Inactive ingredients: silicified microcrystalline cellulose, sodium starch glycolate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate, hypromellose, titanium dioxide, triacetin, D&C yellow 10 aluminum lake, polysorbate 80, and FD&C yellow 6 aluminum lake.

This Medication Guide has been approved by the US Food and Drug Administration.

Distributed by:
Corcept Therapeutics Incorporated
149 Commonwealth Avenue
Menlo Park, CA 94025
Issued: 02/2012


BAR CODE
Each yellow oval-shaped tablet contains 300 mg of mifepristone.
Usual Dosage: For indications, dosage, precautions, etc., see accompanying package insert.
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]
Dispense in tight container (USP)
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN
NDC 76346-073-01
28 Tablets
Rx only
Korlym®
mifepristone
300 mg Tablets
Take tablets whole. Do not split, crush or chew.
ATTENTION PHARMACIST: Dispense attached Medication Guide to each patient
Manufactured for:
Corcept Therapeutics
Menlo Park, CA 94025
Lot No:
Exp.


BAR CODE
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KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN
NDC 76346-073-02
280 Tablets
Rx only
Korlym®
mifepristone
300 mg Tablets
Take tablets whole. Do not split, crush or chew.
ATTENTION PHARMACIST: Dispense attached Medication Guide to each patient.
Manufactured for:
Corcept Therapeutics
Menlo Park, CA 94025
Lot No:
Exp.

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/s/

MARY H PARKS
02/17/2012

EXHIBIT 5

JANSSEN PHARMACEUTICALS

NIZORAL® (KETOCONAZOLE) TABLETS

WARNING:

NIZORAL® Tablets should be used only when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks.

Hepatotoxicity

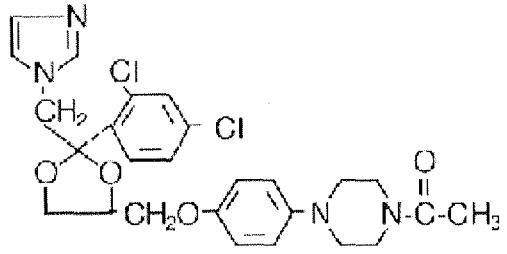
Serious hepatotoxicity, including cases with a fatal outcome or requiring liver transplantation has occurred with the use of oral ketoconazole. Some patients had no obvious risk factors for liver disease. Patients receiving this drug should be informed by the physician of the risk and should be closely monitored. See WARNINGS section.

QT Prolongation and Drug Interactions Leading to QT Prolongation

Co-administration of the following drugs with ketoconazole is contraindicated: dofetilide, quinidine, pimozide, cisapride. Ketoconazole can cause elevated plasma concentrations of these drugs and may prolong QT intervals, sometimes resulting in life-threatening ventricular dysrhythmias such as torsades de pointes. See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions sections.

DESCRIPTION

NIZORAL® is a synthetic broad-spectrum antifungal agent available in scored white tablets, each containing 200 mg ketoconazole base for oral administration. Inactive ingredients are colloidal silicon dioxide, corn starch, lactose, magnesium stearate, microcrystalline cellulose, and povidone. Ketoconazole is cis-1- acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxyl]phenyl] piperazine and has the following structural formula:



Ketoconazole is a white to slightly beige, odorless powder, soluble in acids, with a molecular weight of 531.44.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Mean peak plasma levels of approximately 3.5 μg/mL are reached within 1 to 2 hours, following oral administration of a single 200 mg dose taken with a meal. Subsequent plasma elimination is biphasic with a half-life of 2 hours during the first 10 hours and 8 hours thereafter. Following absorption from the gastrointestinal tract, NIZORAL® is converted into several inactive metabolites. The major identified metabolic pathways are oxidation and degradation of the imidazole and piperazine rings, oxidative O-dealkylation and aromatic hydroxylation. About 13% of the dose is excreted in the urine, of which 2 to 4% is unchanged drug. The major route of excretion is through the bile into the intestinal tract. *In vitro*, the plasma protein binding is about 99% mainly to the albumin fraction. Only a negligible proportion of ketoconazole reaches the cerebrospinal fluid. Ketoconazole is a weak dibasic agent and thus requires acidity for dissolution and absorption.

Electrocardiogram

Pre-clinical electrophysiological studies have shown that ketoconazole inhibits the rapidly activating component of the cardiac delayed rectifier potassium current, prolongs the action potential duration, and may prolong the QT_c interval. Data from some clinical PK/PD studies and drug interaction studies suggest that oral dosing with ketoconazole at 200 mg twice daily for 3-7 days can result in an increase of the QT_c interval: a mean maximum increase of about 6 to 12 msec was seen at ketoconazole peak plasma concentrations about 1-4 hours after ketoconazole administration.

MICROBIOLOGY

Mechanism of Action

Ketoconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14α-demethylase responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane thus weakening the structure and function of the fungal cell membrane.

Activity In Vitro & In Vivo

NIZORAL® Tablets are active against clinical infections with *Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*.

INDICATIONS AND USAGE

NIZORAL® Tablets should be used only when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks.

NIZORAL® (ketoconazole) Tablets are indicated for the treatment of the following systemic fungal infections in patients who have failed or who are intolerant to other therapies: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. NIZORAL® Tablets should not be used for fungal meningitis because it penetrates poorly into the cerebrospinal fluid.

CONTRAINDICATIONS

Drug Interactions

Coadministration of a number of CYP3A4 substrates is contraindicated with NIZORAL® Tablets. Coadministration with ketoconazole can cause elevated plasma concentrations of these drugs and may increase or prolong both therapeutic and adverse effects. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsades de pointes, a potentially fatal arrhythmia. See WARNINGS section, and PRECAUTIONS: Drug Interactions section for specific examples.

Liver Disease

The use of NIZORAL® Tablets is contraindicated in patients with acute or chronic liver disease.

Hypersensitivity

NIZORAL® is contraindicated in patients who have shown hypersensitivity to the drug.

WARNINGS

NIZORAL® Tablets should be used only when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks.

Hepatotoxicity

Serious hepatotoxicity, including cases with a fatal outcome or requiring liver transplantation, has occurred with the use of oral ketoconazole. Some patients had no obvious risk factors for liver disease. Serious hepatotoxicity was reported both by patients receiving high doses for short treatment durations and by patients receiving low doses for long durations.

The hepatic injury has usually, but not always, been reversible upon discontinuation of NIZORAL® Tablets treatment. Cases of hepatitis have been reported in children.

At baseline, obtain laboratory tests (such as SGGT, alkaline phosphatase, ALT, AST, total bilirubin (TBL), Prothrombin Time (PT), International Normalization Ratio (INR), and testing for viral hepatitides). Patients should be advised against alcohol consumption while on treatment. If possible, use of other potentially hepatotoxic drugs should be avoided in patients receiving NIZORAL® Tablets.

Prompt recognition of liver injury is essential. During the course of treatment, serum ALT should be monitored weekly for the duration of treatment. If ALT values increase to a level above the upper limit of normal or 30 percent above baseline, or if the patient develops symptoms, ketoconazole treatment should be interrupted and a full set of liver tests should be obtained. Liver tests should be repeated to ensure normalization of values. Hepatotoxicity has been reported with restarting oral ketoconazole (rechallenge). If it is decided to restart oral ketoconazole, monitor the patient frequently to detect any recurring liver injury from the drug.

QT Prolongation and Drug Interactions Leading to QT Prolongation

Ketoconazole can prolong the QT interval. Co-administration of the following drugs with ketoconazole is contraindicated: dofetilide, quinidine, pimozide, and cisapride. Ketoconazole can cause elevated plasma concentrations of these drugs which may prolong the QT interval, sometimes resulting in life-threatening ventricular dysrhythmias such as torsades de pointes.

Adrenal Insufficiency

NIZORAL® Tablets decrease adrenal corticosteroid secretion at doses of 400 mg and higher. This effect is not shared with other azoles. The recommended dose of 200 mg - 400 mg daily should not be exceeded.

Adrenal function should be monitored in patients with adrenal insufficiency or with borderline adrenal function and in patients under prolonged periods of stress (major surgery, intensive care, etc.).

Adverse Reactions Associated with Unapproved Uses

Ketoconazole has been used in high doses for the treatment of advanced prostate cancer and for Cushing's syndrome when other treatment options have failed. The safety and effectiveness of ketoconazole have not been established in these settings and the use of ketoconazole for these indications is not approved by FDA.

In a clinical trial involving 350 patients with metastatic prostatic cancer, eleven deaths were reported within two weeks of starting treatment with high doses of ketoconazole

tablets (1200 mg/day). It is not possible to ascertain from the information available whether death was related to ketoconazole therapy or adrenal insufficiency in these patients with serious underlying disease.

Hypersensitivity

Anaphylaxis has been reported after the first dose. Several cases of hypersensitivity reactions including urticaria have also been reported.

Enhanced Sedation

Co-administration of NIZORAL® Tablets with oral midazolam, oral triazolam or alprazolam has resulted in elevated plasma concentrations of these drugs. This may potentiate and prolong hypnotic and sedative effects, especially with repeated dosing or chronic administration of these agents. Concomitant administration of NIZORAL® Tablets with oral triazolam, oral midazolam, or alprazolam is contraindicated. (See CONTRAINDICATIONS and PRECAUTIONS: Drug Interactions sections.)

Myopathy

Co-administration of CYP3A4 metabolized HMG-CoA reductase inhibitors such as simvastatin, and lovastatin is contraindicated with NIZORAL® Tablets. (See CONTRAINDICATIONS and PRECAUTIONS: Drug Interactions sections.)

PRECAUTIONS

General

NIZORAL® Tablets have been demonstrated to lower serum testosterone. Once therapy with NIZORAL® Tablets has been discontinued, serum testosterone levels return to baseline values. Testosterone levels are impaired with doses of 800 mg per day and abolished by 1600 mg per day. Clinical manifestations of decreased testosterone concentrations may include gynecomastia, impotence and oligospermia.

Information for Patients

Patients should be instructed to report any signs and symptoms which may suggest liver dysfunction so that appropriate biochemical testing can be done. Such signs and symptoms may include unusual fatigue, anorexia, nausea and/or vomiting, abdominal pain, jaundice, dark urine or pale stools (see WARNINGS section).

Drug Interactions

Drugs that affect the absorption, distribution, metabolism, and excretion of ketoconazole may alter the plasma concentrations of ketoconazole. For example, gastric acid suppressants (e.g., antacids, histamine H_2-blockers, proton pump inhibitors) have been shown to reduce plasma concentrations of ketoconazole.

Ketoconazole is a substrate and potent inhibitor of CYP3A4. Therefore, the following drug interactions may occur when NIZORAL® is co-administered with other drugs that interact with CYP3A4. (See Table 1 and Table 2 for an overview of these drug interactions; details are provided in the text that follows these tables.)

1. NIZORAL® may decrease the elimination of drugs metabolized by CYP3A4, thereby increasing their plasma concentrations. Increased exposure to these drugs may cause an increase or prolongation of their therapeutic and/or adverse effects. Concomitant use with NIZORAL® Tablets is contraindicated for drugs known to present a risk of serious side effects with increased exposure (see BOXED WARNING, CONTRAINDICATIONS section, and PRECAUTIONS: Drug Interactions, Table 1). For others, monitoring of plasma concentrations is advised when possible. Clinical signs and symptoms associated with these drugs should be monitored, with dosage adjusted as needed.

2. Inducers of CYP3A4 may decrease the plasma concentrations of ketoconazole (see Table 2). NIZORAL® may not be effective in patients concomitantly taking one of these drugs. Therefore, administration of these drugs with NIZORAL® is not recommended.

3. Other inhibitors of CYP3A4 may increase the plasma concentrations of ketoconazole (see Table 2). Patients who must take NIZORAL® concomitantly with one of these drugs should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of NIZORAL®.

Table 1. Selected Drugs That Have Been Shown To or Are Predicted To Have Their Plasma Concentrations Altered By NIZORAL®*	
Systemic exposure to these drugs is increased significantly by the addition of ketoconazole: **Concomitant use with ketoconazole is *contraindicated.***	
Alprazolam, midazolam, triazolam	HMG-CoA reductase inhibitors (lovastatin, simvastatin)
Cisapride	Nisoldipine
Dofetilide	Pimozide

Eplerenone	Quinidine
Ergot alkaloids (ergotamine, dihydroergotamine)	
Systemic exposure to these drugs is increased by ketoconazole: Careful monitoring, with possible adjustment in dosage, is recommended.	
Alfentanil, fentanyl, sulfentanil	Indinavir, saquinavir
Amlodipine, felodipine, nicardipine, nifedipine	Methylprednisolone
Bosentan	Rifabutin
Buspirone	Sildenafil
Busulfan	Sirolimus (co-administration not recommended)
Carbamazepine	Tacrolimus
Cilostazol	Telithromycin
Cyclosporine	Tolterodine
Digoxin	Trimetrexate
Docetaxel, paclitaxel	Verapamil
Oral anti-coagulants	Vinca alkaloids (vincristine, -vinblastine, vinorelbine)

* This list is not all-inclusive.

Table 2. Selected Drugs That Have Been Shown To or Are Predicted To Alter The Plasma Concentration Of NIZORAL®	
Systemic exposure to ketoconazole is reduced significantly by these drugs: Concomitant use with ketoconazole is not recommended.	
Carbamazepine	Phenytoin
Gastric Acid Suppressants (antacids, antimuscarinics, histamine H_2-blockers, proton pump inhibitors, sucralfate)	Rifampin, rifabutin, isoniazid
Nevirapine	
Systemic exposure to ketoconazole is increased significantly by this drug: Dose reduction of ketoconazole should be considered	
Ritonavir	

* This list is not all-inclusive.

1. Effects of ketoconazole on other drugs

1.1 Systemic exposure to the following drugs is significantly increased by co-administration of ketoconazole. **Concomitant use of these drugs with NIZORAL® Tablets is contraindicated:**

Alprazolam, midazolam, triazolam

Co-administration of NIZORAL® Tablets with alprazolam, midazolam, or triazolam has resulted in elevated plasma concentrations of these drugs. This may potentiate and prolong hypnotic and sedative effects, especially with repeated or chronic administration of these agents. Concomitant administration of NIZORAL® Tablets with alprazolam, oral midazolam, and oral triazolam is contraindicated. (See CONTRAINDICATIONS and WARNINGS sections.) Special precaution and patient monitoring are required with concomitant parenteral midazolam, because the sedative effect may be prolonged.

Cisapride

Oral ketoconazole potently inhibits the metabolism of cisapride resulting in a mean eight-fold increase in AUC of cisapride, which can lead to prolongation of QT interval. Therefore concomitant administration of NIZORAL® Tablets with

cisapride is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS sections.)

Dofetilide

The class III antiarrhythmic dofetilide is known to prolong the QT interval. The potential increase in dofetilide plasma concentrations when administered concomitantly with ketoconazole could result in serious cardiovascular events including QT_c prolongation and rare occurrences of torsades de pointes. Therefore, concomitant administration of NIZORAL® Tablets with dofetilide is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS sections.)

Eplerenone

Ketoconazole increases the eplerenone AUC by roughly 5-fold, thereby increasing the risk for hyperkalemia and hypotension. Co-administration of NIZORAL® and eplerenone is contraindicated. (See CONTRAINDICATIONS section.)

Ergot Alkaloids

Elevated concentrations of ergot alkaloids can cause ergotism, i.e., a risk for vasospasm potentially leading to cerebral ischemia and/or ischemia of the extremities. Concomitant administration of ergot alkaloids such as dihydroergotamine and ergotamine with NIZORAL® Tablets is contraindicated. (See CONTRAINDICATIONS section.)

HMG-CoA Enzyme Inhibitors (lovastatin, simvastatin)

Co-administration of ketoconazole with CYP3A4-metabolized HMG-CoA reductase inhibitors such as simvastatin, and lovastatin, may increase the risk of skeletal muscle toxicity, including rhabdomyolysis. Concomitant administration of NIZORAL® Tablets with these HMG-CoA reductase inhibitors is contraindicated. (See CONTRAINDICATIONS and WARNINGS sections.)

Nisoldipine

Pre-treatment with and concomitant administration of ketoconazole resulted in a 24-fold and 11-fold increase in mean AUC and C_{max} of nisoldipine, respectively, compared with treatment with nisoldipine 5 mg alone. Concomitant administration of ketoconazole with nisoldipine is contraindicated. (See CONTRAINDICATIONS section.)

Pimozide

Pimozide is known to prolong the QT interval and is partially metabolized by CYP3A4. Co-administration of NIZORAL® and pimozide could result in serious cardiovascular events including QT_c prolongation and rare occurrences of torsades de pointes, and is therefore contraindicated. (See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS sections.)

Quinidine

The class IA antiarhythmic quinidine is known to prolong the QT interval. The potential increase in quinidine plasma concentrations when administered concomitantly with ketoconazole could result in serious cardiovascular events including QT_c prolongation and rare occurrences of torsades de pointes. Therefore, concomitant administration of NIZORAL® Tablets with quinidine is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS sections.)

1.2. Co-administration of ketoconazole with the following agents was shown or is expected to result in increased exposure to these drugs. Therefore, careful monitoring of plasma concentrations or adverse events of these drugs is recommended. Adjustment of dosage of these drugs may be needed.

Alfentanil, sufentanil, fentanyl

In vitro data suggest that alfentanil, sufentanil and fentanyl are metabolized by CYP3A4. Concomitant administration of NIZORAL® Tablets and alfentanil, sufentanil, or fentanyl may increase plasma concentrations of the latter drugs.

Amlodipine, felodipine, nicardipine, nifedipine

CYP3A4 metabolized calcium channel blockers such as amlodipine, felodipine, nicardipine, and nifedipine should be used cautiously with NIZORAL® Tablets as ketoconazole may cause several-fold increases in plasma concentrations of these calcium channel blockers.

Bosentan

Concomitant administration of ketoconazole increased the C_{max} and AUC of bosentan 2.1- and 2.3 – fold, respectively. No dosage adjustment of bosentan is needed but close monitoring for increased bosentan-associated adverse effects is recommended.

Buspirone

Concomitant administration of buspirone with ketoconazole may result in significant increases in plasma concentrations of buspirone. When administered

with NIZORAL® Tablets, a low initial dose of buspirone with subsequent dosage adjustment based on clinical assessment is recommended.

Busulfan

NIZORAL® Tablets may decrease the clearance and thus increase the systemic exposure to busulfan.

Carbamazepine

In vivo studies have demonstrated an increase in plasma carbamazepine concentrations in subjects concomitantly receiving ketoconazole. Close monitoring of plasma carbamazepine concentrations is recommended whenever ketoconazole is given to patients stabilized on carbamazepine therapy.

Cilostazol

Ketoconazole had been shown to increase both cilostazol AUC and C_{max} by about two-fold when administered concurrently. Co-administration of ketoconazole with cilostazol resulted in increased incidences of adverse effects, such as headache. When NIZORAL® Tablets is administered concomitantly with cilostazol, the prescriber should consider up to a 50% reduction in cilostazol dosage.

Cyclosporine

Ketoconazole tablets may alter the metabolism of cyclosporine, thereby resulting in elevated cyclosporine plasma concentrations. Dosage adjustment may be required if cyclosporine or tacrolimus is given concomitantly with NIZORAL® Tablets.

Digoxin

Rare cases of elevated plasma concentrations of digoxin have been reported. It is not clear whether this was due to the combination of therapy. It is, therefore, advisable to monitor digoxin concentrations in patients receiving ketoconazole.

Docetaxel

In the presence of ketoconazole, the clearance of docetaxel in cancer patients was shown to decrease by 50%. When docetaxel and NIZORAL® are administered together, dosage reduction in docetaxel may be necessary in order to minimize the incidence of toxicities associated with docetaxel.

Indinavir, saquinavir

Concomitant administration of NIZORAL® and protease inhibitors metabolized by CYP3A4, such as indinavir and saquinavir, may increase plasma concentrations of these protease inhibitors. Dosage reduction of indinavir is recommended when administering ketoconazole concomitantly. No dosage

adjustments are recommended when saquinavir and ketoconazole are co-administered for a short period of time.

Methylprednisolone

NIZORAL® Tablets may alter the metabolism of methylprednisolone, resulting in elevated plasma concentrations of methylprednisolone. Dose adjustments may be required if methylprednisolone is given concomitantly with NIZORAL® Tablets.

Oral anti-coagulants

Oral imidazole compounds such as ketoconazole may enhance the anticoagulant effect of coumarin-like drugs, thus the anticoagulant effect should be carefully titrated and monitored.

Oral hypoglycemic agents

Because severe hypoglycemia has been reported in patients concomitantly receiving oral miconazole (an imidazole) and oral hypoglycemic agents, such a potential interaction involving the latter agents when used concomitantly with ketoconazole tablets (an imidazole) cannot be ruled out.

Rifabutin

Ketoconazole was shown to inhibit the CYP-mediated metabolism of rifabutin *in vitro*. Co-administration with NIZORAL® Tablets may result in elevated plasma concentrations of rifabutin.

Sildenafil

Ketoconazole had been shown to increase sildenafil plasma concentrations. When used concomitantly with NIZORAL® Tablets, a 50% reduction in sildenafil starting dose should be considered.

Sirolimus

Multiple-dose ketoconazole had been shown to increase sirolimus C_{max} and AUC by 4.3-fold and 10.9-fold, respectively. The concomitant use of NIZORAL® Tablets and sirolimus is not recommended.

Tacrolimus

Ketoconazole had been shown to decrease the oral clearance of tacrolimus thereby leading to a 2-fold increase in tacrolimus oral bioavailability. Adjustment in tacrolimus dosage may be required if tacrolimus is given concomitantly with NIZORAL® Tablets.

Telithromycin

Ketoconazole increased the AUC of telithromycin by 1.5 to 2-fold. Use caution when administering telithromycin concurrently with NIZORAL® Tablets since this may result in an increased risk for telithromycin associated adverse events.

Tolterodine

In the presence of ketoconazole, the apparent oral clearance of tolterodine decreased resulting in at least a two-fold increase in tolterodine. For patients receiving ketoconazole, a 50% reduction in the initial tolterodine dosage is recommended.

Trimetrexate

In vitro data suggest that trimetrexate is extensively metabolized by CYP3A4. *In vitro* animal models have demonstrated that ketoconazole potently inhibits the metabolism of trimetrexate. Patients treated concomitantly with trimetrexate and NIZORAL® Tablets should be carefully monitored for trimetrexate-associated toxicities.

Verapamil

Findings of *in vitro* metabolic studies indicate that verapamil is metabolized by enzymes including CYP3A4. Ketoconazole may increase verapamil serum concentrations. Caution should be taken when co-administering verapamil with NIZORAL® Tablets.

Vinca Alkaloids (vincristine, vinblastine, vinorelbine)

NIZORAL® may inhibit the metabolism of vinca alkaloids metabolized by CYP3A4. Close monitoring for toxicities associated with vincristine, vinblastine, or vinorelbine is recommended when co-administered with NIZORAL® Tablets.

2. Effects of other drugs on ketoconazole

2.1 Drugs affecting the absorption of ketoconazole

Gastric Acid Suppressors/Neutralizers

Studies have shown that absorption of ketoconazole is impaired when gastric acid production is decreased. Reduced plasma concentrations of ketoconazole were reported when NIZORAL® Tablets were administered with antacids, antimuscarinics, histamine H_2-blockers, proton pump inhibitors (omeprazole, lansoprazole) and sucralfate. (See PRECAUTIONS, Drug Interactions (General) section.)

2.2 *Drugs that were shown or are expected to significantly reduce the systemic exposure to ketoconazole*

Co-administration of ketoconazole with potent CYP3A4 enzyme inducers is not recommended.

Carbamazepine

Concomitant administration of ketoconazole tablets with carbamazepine may alter the metabolism of one or both of the drugs. Close monitoring for both plasma concentrations of carbamazepine and reduced ketoconazole efficacy is recommended.

Nevirapine

Ketoconazole AUC and C_{max} decreased by a median of 63% and 40%, respectively, in HIV-infected patients who were given nevirapine 200 mg once daily for two weeks along with ketoconazole 400 mg daily. Concomitant administration of NIZORAL® Tablets and nevirapine is not recommended.

Phenytoin

Concomitant administration of ketoconazole with phenytoin may alter the metabolism of one or both of the drugs. Close monitoring for both plasma concentrations of phenytoin and reduced efficacy of NIZORAL® Tablets is recommended.

Rifampin, rifabutin, isoniazid

Concomitant administration of rifampin and rifabutin with ketoconazole tablets reduces the blood concentrations of the latter. INH (Isoniazid) was also reported to affect ketoconazole concentrations adversely. These antitubercular drugs should not be given concomitantly with NIZORAL® Tablets.

2.3 *Drugs that significantly increase the systemic exposure to ketoconazole*

Ritonavir

Concomitant administration of ritonavir with ketoconazole tablets increases was shown to increase the oral bioavailability of ketoconazole. Therefore, when ritonavir is to be given concomitantly, higher doses (>200 mg/day) of NIZORAL® Tablets should not be used.

3. Other drug interactions

Alcohol

Rare cases of a disulfiram-like reaction to alcohol have been reported. These experiences have been characterized by flushing, rash, peripheral edema, nausea, and headache. Symptoms resolved within a few hours.

Loratadine

After the co-administration of 200 mg oral ketoconazole twice daily and one 20 mg dose of loratadine to 11 subjects, the AUC and C_{max} of loratadine averaged 302% (±142 S.D.) and 251% (± 68 S.D.), respectively, of those obtained after co-treatment with placebo. The AUC and C_{max} of descarboethoxyloratadine, an active metabolite, averaged 155% (± 27 S.D.) and 141% (± 35 S.D.), respectively. However, no related changes were noted in the QT_c on ECG taken at 2, 6, and 24 hours after the coadministration. Also, there were no clinically significant differences in adverse events when loratadine was administered with or without ketoconazole.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Ketoconazole did not show any signs of mutagenic potential when evaluated using the dominant lethal mutation test or the *Ames Salmonella* microsomal activator assay. Ketoconazole was not carcinogenic in an 18-month, oral study in Swiss albino mice or a 24-month oral carcinogenicity study in Wistar rats at dose levels of 5, 20 and 80 mg/kg/day. The high dose in these studies was approximately 1x (mouse) or 2x (rat) the clinical dose in humans based on a mg/m^2 comparison.

Pregnancy

Teratogenic effects: *Pregnancy Category C:* Ketoconazole has been shown to be teratogenic (syndactylia and oligodactylia) in the rat when given in the diet at 80 mg/kg/day (2 times the maximum recommended human dose, based on body surface area comparisons). However, these effects may be related to maternal toxicity, evidence of which also was seen at this and higher dose levels.

There are no adequate and well controlled studies in pregnant women. NIZORAL® Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Ketoconazole has also been found to be embryotoxic in the rat when given in the diet at doses higher than 80 mg/kg during the first trimester of gestation.

In addition, dystocia (difficult labor) was noted in rats administered oral ketoconazole during the third trimester of gestation. This occurred when ketoconazole was administered at doses higher than 10 mg/kg (about one fourth the maximum human dose, based on body surface area comparison).

Nursing Mothers

Ketoconazole has been shown to be excreted in the milk. Mothers who are under treatment with NIZORAL® Tablets should not breast feed.

Pediatric Use

NIZORAL® Tablets have not been systematically studied in children of any age, and essentially no information is available on children under 2 years. NIZORAL® Tablets should not be used in pediatric patients unless the potential benefit outweighs the risks.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following adverse reactions were reported in clinical trials:

Immune System Disorders: anaphylactoid reaction

Endocrine Disorders: gynecomastia

Metabolism and Nutrition Disorders: alcohol intolerance, anorexia, hyperlipidemia, increased appetite

Psychiatric Disorders: insomnia, nervousness

Nervous System Disorders: headache, dizziness, paresthesia, somnolence

Eye Disorders: photophobia

Vascular Disorders: orthostatic hypotension

Respiratory, Thoracic and Mediastinal Disorders: epistaxis

Gastrointestinal Disorders: vomiting, diarrhea, nausea, constipation, abdominal pain, abdominal pain upper, dry mouth, dysgeusia, dyspepsia, flatulence, tongue discoloration

Hepatobiliary Disorders: hepatitis, jaundice, hepatic function abnormal

Skin and Subcutaneous Tissues Disorders: erythema multiforme, rash, dermatitis, erythema, urticaria, pruritus, alopecia, xeroderma

Musculoskeletal and Connective Tissue Disorders: myalgia

Reproductive System and Breast Disorders: menstrual disorder

General Disorders and Administration Site Conditions: asthenia, fatigue, hot flush, malaise, edema peripheral, pyrexia, chills

Investigations: platelet count decreased.

Post-Marketing Experience

The following adverse reactions have been identified during postapproval use of Nizoral tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions were reported during post-marketing experience:

Blood and Lymphatic System Disorders: thrombocytopenia

Immune System Disorders: allergic conditions including anaphylactic shock, anaphylactic reaction, angioneurotic edema

Endocrine Disorders: adrenocortical insufficiency

Nervous System Disorders: reversible intracranial pressure increased (e.g. papilloedema, fontanelle bulging in infants)

Hepatobiliary Disorders: serious hepatotoxicity including hepatitis cholestatic, biopsy-confirmed hepatic necrosis, cirrhosis, hepatic failure including cases resulting in transplantation or death

Skin and Subcutaneous Tissue Disorders: acute generalized exanthematous pustulosis, photosensitivity

Musculoskeletal and Connective Tissue Disorders: arthralgia

Reproductive System and Breast Disorders: erectile dysfunction; with doses higher than the recommended therapeutic dose of 200 or 400mg daily, azoospermia.

OVERDOSAGE

In the event of acute accidental overdose, treatment consists of supportive and symptomatic measures. Within the first hour after ingestion, activated charcoal may be administered.

DOSAGE AND ADMINISTRATION

There should be laboratory as well as clinical documentation of infection prior to starting ketoconazole therapy. The usual duration of therapy for systemic infection is 6 months. Treatment should be continued until active fungal infection has subsided.

Adults

The recommended starting dose of NIZORAL® (ketoconazole) Tablets is a single daily administration of 200 mg (one tablet). If clinical responsiveness is insufficient within the expected time, the dose of NIZORAL® Tablets may be increased to 400 mg (two tablets) once daily.

Children

In small numbers of children over 2 years of age, a single daily dose of 3.3 to 6.6 mg/kg has been used. NIZORAL® Tablets have not been studied in children under 2 years of age.

HOW SUPPLIED

NIZORAL® (ketoconazole) is available as white, scored tablets containing 200 mg of ketoconazole debossed "JANSSEN" and on the reverse side debossed "NIZORAL". They are supplied in bottles of 100 tablets (NDC 50458-220-10).

Store at controlled room temperature 15°-25°C (59°-77°F).

Protect from moisture.

Keep out of reach of children.

Rev.
Janssen Pharmaceuticals, Inc,
Titusville, New Jersey 08560

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MEDICATION GUIDE
NIZORAL®
(ketoconazole)
Tablets

What is the most important information I should know about NIZORAL® Tablets?

NIZORAL® Tablets is not the only medicine available to treat fungal infections and should only be used when other medicines are not right for you. Talk to your healthcare provider to find out if NIZORAL® Tablets are right for you.

NIZORAL® Tablets can cause serious side effects, including:

- **liver problems (hepatotoxicity). Some people who were treated with ketoconazole the active ingredient in NIZORAL® Tablets, had serious liver problems that led to death or the need for a liver transplant.** Call your healthcare provider right away if you have any of the following symptoms:
  - loss of appetite or start losing weight (anorexia)
  - nausea or vomiting
  - feel tired
  - stomach pain or tenderness
  - dark urine or light colored stools
  - yellowing of your skin or the whites of your eyes
  - fever or rash
- **changes in the electrical activity of your heart called QT prolongation. QT prolongation can cause irregular heart beats that can be life threatening.** This can happen when NIZORAL® Tablets are taken with certain medicines, such as dofetilide, quinidine, pimozide, and cisapride. Talk to your healthcare provider about other medicines you are taking before you start taking NIZORAL® Tablets. Tell your healthcare provider right away if you feel faint, lightheaded, dizzy, or feel your heart beating irregularly or fast. These may be symptoms related to QT prolongation.

What are NIZORAL® Tablets?

- NIZORAL® Tablets are prescription medicine used to treat serious fungal infections including: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis.
- NIZORAL® Tablets are not for people with fungal nail infections.
- NIZORAL® Tablets have not been approved for the treatment of advanced prostate cancer or Cushing's syndrome. The safety and efficacy have not been established.
- NIZORAL® Tablets should only be used in children if prescribed by the healthcare provider who has determined that the benefits outweigh the risks.

Who should not take NIZORAL® Tablets?

- **Do not take NIZORAL® Tablets if you:**
  - have liver problems
  - take simvastatin, and lovastatin. NIZORAL® Tablets when taken with these medicines may cause muscle problems.
  - take eplerenone, dihydroergotamine, ergotamine, and nisoldipine.
  - take triazolam, midazolam, or alprazolam. Taking NIZORAL® Tablets with these medicines may make you very drowsy and make your drowsiness last longer.
  - are allergic to ketoconazole or any of the ingredients in NIZORAL® Tablets. See the end of this Medication Guide for a complete list of ingredients in NIZORAL® Tablets.

Before you take NIZORAL® Tablets, tell your healthcare provider if you:

- have had an abnormal heart rhythm tracing (ECG) or anyone in your family have or have had a heart problem called "congenital long QT syndrome".
- have adrenal insufficiency.
- are pregnant or plan to become pregnant. It is not known if NIZORAL® Tablets will harm your unborn baby.
- are breastfeeding or plan to breastfeed. NIZORAL® Tablets can pass into your breast milk. You and your healthcare provider should decide if you will take NIZORAL®

Tablets or breastfeed. You should **NOT** do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Using NIZORAL® Tablets with certain other medicines may affect each other. Using NIZORAL® Tablets with other medicines can cause serious side effects.

How should I take NIZORAL® Tablets?

- Take NIZORAL® 1 time each day.
- Do not stop taking NIZORAL® Tablets without first talking to your healthcare provider.

What should I avoid while taking NIZORAL® Tablets?

- Do not drink alcohol while taking NIZORAL® Tablets.

What are the possible side effects of NIZORAL® Tablets?

NIZORAL® Tablets may cause serious side effects, including:

- **See "What is the most important information I should know about NIZORAL® Tablets?"**
- **adrenal insufficiency.** Adrenal insufficiency is a condition in which the adrenal glands do not make enough steroid hormones. NIZORAL® Tablets may cause adrenal insufficiency if you take a high dose. Your healthcare provider will follow you closely if you have adrenal insufficiency or if you are taking prednisone or other similar medicines for long periods of time. Call your healthcare provider right away if you have symptoms of adrenal insufficiency such as tiredness, weakness, dizziness, nausea, and vomiting.
- **serious allergic reactions.** Some people can have a serious allergic reaction to NIZORAL® Tablets. Stop taking NIZORAL® Tablets and go to the nearest hospital emergency room right away if you get a rash, itching, hives, fever, swelling of the lips or tongue, chest pain, or have trouble breathing. These could be signs of a serious allergic reaction.
- **muscle problems.** Taking certain medicines with NIZORAL® Tablets may cause muscle problems. See **"Who should not take NIZORAL® Tablets?"**

The most common side effects of NIZORAL® Tablets include nausea, headache,

diarrhea, stomach pain, and abnormal liver function tests.

These are not all the possible side effects of NIZORAL® Tablets. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NIZORAL® Tablets?

- Store NIZORAL® Tablets at room temperature between 59°F to 77°F (15°C to 25°C).
- Keep NIZORAL® Tablets dry.

General information about the safe and effective use of NIZORAL® Tablets.

Medications are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NIZORAL® Tablets for a condition for which it was not prescribed. Do not give NIZORAL® Tablets to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about NIZORAL® Tablets.

If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about NIZORAL® Tablets that is written for health professionals.

What are the ingredients in NIZORAL® Tablets?

Active ingredient: ketoconazole.

Inactive ingredients: colloidal silicon dioxide, corn starch, lactose, magnesium stearate, microcrystalline cellulose, and povidone.

Issued : (07/2013)

This Medication Guide has been approved by the U.S. Food and Drug Administration

EXHIBIT 6

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2009, p. 609–614 Vol. 53, No. 2
0066-4804/09/$08.00+0 doi:10.1128/AAC.00769-08

Drug-Drug Interaction Study of Ketoconazole and Ritonavir-Boosted Saquinavir[▽]

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Received 12 June 2008/Returned for modification 28 September 2008/Accepted 8 November 2008

Saquinavir, a potent human immunodeficiency virus protease inhibitor, is extensively metabolized by CYP3A4. Saquinavir is coadministered with ritonavir, a strong CYP3A4 inhibitor, to boost its exposure. Ketoconazole is a potent CYP3A inhibitor. The objectives of this study were to investigate the effect of ketoconazole on the pharmacokinetics of saquinavir/ritonavir and vice versa using the approved dosage regimens of saquinavir/ritonavir at 1,000/100 mg twice daily and ketoconazole at 200 mg once daily. This was an open-label, randomized two-arm, one-sequence, two-period crossover study in healthy subjects. In study arm 1, 20 subjects received saquinavir/ritonavir treatment alone for 14 days, followed in combination with ketoconazole treatment for 14 days. In arm 2, 12 subjects received ketoconazole treatment for 6 days, followed in combination with saquinavir/ritonavir treatment for 14 days. The pharmacokinetics were assessed on the last day of each treatment (days 14 and 28 in arm 1 and days 6 and 20 in arm 2). The exposures C_{max} and the area under the concentration-time curve from 0 to 12 h (AUC_{0-12}) of saquinavir and ritonavir with or without ketoconazole were not substantially altered after 2 weeks of concomitant dosing with ketoconazole. The C_{max} and AUC_{0-12} of ketoconazole, dosed at 200 mg once daily, were increased by 45% (90% confidence interval = 32 to 59%) and 168% (90% confidence interval = 146 to 193%), respectively, after 2 weeks of concomitant dosing with ritonavir-boosted saquinavir (1,000 mg of saquinavir/100 mg of ritonavir given twice daily). The greater exposure to ketoconazole when given in combination with saquinavir/ritonavir was not associated with unacceptable safety or tolerability. No dose adjustment for saquinavir/ritonavir (1,000/100 mg twice daily) is required when coadministered with 200 mg of ketoconazole once daily, and high doses of ketoconazole (>200 mg/day) are not recommended.

Saquinavir, a potent human immunodeficiency virus (HIV) protease inhibitor, is extensively metabolized by cytochrome P450 (CYP3A4; see the product information for Invirase capsules and tablets [Hoffman-La Roche, Inc.]). For the antiretroviral combination treatment of HIV-infected patients, saquinavir is coadministered with ritonavir, another HIV protease inhibitor and strong CYP3A4 inhibitor (see the product information for the Norvir 100-mg capsule [Abbott Laboratories]), to boost the exposure of saquinavir. The new dosage form of saquinavir (Invirase), a 500-mg film-coated tablet, was approved in 2004 in the United States and 2005 in Europe and allows a lower pill burden using the dosing regimen of saquinavir/ritonavir at 1,000/100 mg twice daily, which was approved in 2003. Saquinavir exhibits a pronounced food effect, and patients are advised to take saquinavir with ritonavir always with a full meal (according to the product information for Invirase capsules and tablets [Hoffman-La Roche, Inc.]). The imidazole antifungal compound ketoconazole is effective in the treatment of oropharyngeal candidiasis, the most common infection among persons infected with HIV (1). Ketoconazole is also known as a prototypic and strong CYP3A4 inhibitor (2) and is a recommended drug of choice for investigating the interaction with CYP3A4 substrates such as saquinavir (5). It has already been shown that coadministration of ketoconazole at 200 or 400 mg once daily with saquinavir/ritonavir at 400/400 mg twice daily resulted in increased area under the drug plasma concentration-time curve (AUC) and peak plasma concentrations (C_{max}) for saquinavir and ritonavir, whereas the effect of saquinavir/ritonavir on the pharmacokinetics of ketoconazole was not evaluated (4). The present study was performed using the approved dosing regimens of saquinavir/ritonavir at 1,000/100 mg twice daily and ketoconazole at 200 mg once daily and documents the drug-drug interaction after 2 weeks of concomitant dosing in both directions, i.e., the effect of ketoconazole on the pharmacokinetics of saquinavir/ritonavir and that of saquinavir/ritonavir on ketoconazole. The objective of the study was to provide appropriate dosing guidelines to clinicians who treat HIV patients with saquinavir/ritonavir and ketoconazole.

MATERIALS AND METHODS

Study design and population. This was an open-label, randomized two-arm, one-sequence, two-period crossover study conducted in healthy male and female subjects. Subjects had to give written informed consent, and the study protocol was approved by the IRB Institutional Review Board (Comité Consultatif de Protections des Personnes dans la Recherche Biomédicale, Strasbourg, France). The study was conducted in full compliance with the principles of the Declaration of Helsinki III and performed according to the guidelines of Good Clinical Practice.

In order to enable stable pharmacokinetic conditions for saquinavir/ritonavir, the combination of these two drugs was administered for 2 weeks. ketoconazole

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▽ Published ahead of print on 17 November 2008.

alone was dosed for 6 days, and the combination of ritonavir/saquinavir with ketoconazole was administered in both study arms for another 2 weeks. In study arm 1, saquinavir/ritonavir was administered first (period 1), followed by the addition of ketoconazole (period 2), and in study arm 2, ketoconazole was dosed first (period 1), followed by the addition of saquinavir/ritonavir (period 2). The planned sample size for study arm 1 was $n = 20$, assuming a within-subject coefficient of variation (CV) of up to 30% for the saquinavir AUC and C_{max}, which was based on the observed within-subject CV of 23 and 24% for these parameters, respectively, from a previous study (BP17359 [Roche data on file]). For study arm 2, the sample size was set to $n = 12$, assuming a within-subject CV of up to 16% for the ketoconazole AUC and C_{max} based on the respective values of 16 and 14% observed in a previous study (WK14435 [Roche data on file]). These sample sizes would ensure, that, with a probability of at least 80%, the two-sided 90% confidence interval (CI) for the geometric population mean of the individual parameter ratios (period 2/period 1) would be within 75 to 133% of the geometric population mean for saquinavir and within 80 to 125% of the geometric population mean for ketoconazole. Subjects were randomized in study arms 1 and 2 with a block size of eight (five to arm 1, three to arm 2).

Subjects underwent screening evaluations to determine eligibility within 28 days prior to study enrollment. Screening procedures included, among others, tests for HIV, tests for hepatitis B and C, and tests for pregnancy in women. Healthy male and female subjects, aged 18 to 65 years (inclusive) with body mass indexes between 18 to 30 kg/m^2 and being nonsmokers, were enrolled into the study. Intake of grapefruit or grapefruit juice was not allowed from 2 weeks prior to the first dose and during the study. In addition, the consumption of alcohol was not permitted during the study. Subjects were instructed to take the study drugs always with a meal. No concomitant medications were permitted during the study except to treat adverse events. Subjects who were on concomitant treatment with drugs known as CYP3A4 substrates, CYP3A4 inhibitors, or CYP3A4 inducers were excluded from the study. Women in the study had to be of non-child-bearing potential or under efficient nonhormonal contraception throughout the study and until at least 1 month thereafter.

In study arm 1, saquinavir/ritonavir at 1,000/100 mg was dosed twice daily for 28 days (excluding the evening dose on day 14), with ketoconazole at 200 mg once daily added from days 15 to 28 (period 1, days 1 to 14; period 2, days 15 to 28). In study arm 2, ketoconazole at 200 mg was dosed once daily for 20 days with saquinavir/ritonavir at 1,000/100 mg twice daily added from days 7 to 20 (period 1, day 1 to 6; period 2, day 7 to 20). In study arm 1 the pharmacokinetics were assessed for saquinavir/ritonavir over 12 h on days 14 and 28, and in arm 2 the pharmacokinetics were assessed for ketoconazole over 24 h on days 6 and 20. Study drugs were administered 30 min after the start of a standard high-fat, high-calorie breakfast (63 g of fat, 975 kcal) on days 14 and 28 for arm 1 or days 6 and 20 for arm 2. Plasma samples for pharmacokinetic assessments were collected predose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, and 24 h postdose (13 samples). In study arm 1, subjects received on days 14 and 28 saquinavir and ritonavir doses only in the morning. In study arm 1, plasma samples were analyzed for saquinavir and ritonavir, and in study arm 2 plasma samples were analyzed for ketoconazole. In both study arms additional predose concentration measurements were made on the last 2 to 4 days of periods 1 and 2 to document stable pharmacokinetic conditions. In study arms 1 and 2, during both pharmacokinetic assessment periods, subjects were confined to the study center. Safety parameters included medical history, physical examinations, standard safety laboratory assessments (hematology, blood chemistry, and urinalysis), vital signs, and serial electrocardiograms recorded at prespecified time points throughout the trial, as well as urine analyses for drugs of abuse, alcohol breath tests, and urine pregnancy tests (in females only). A medical follow-up examination was conducted 15 to 21 days after the last dose of study drugs. All subjects were observed for adverse events during the entire study period.

Bioanalysis. For the determination of saquinavir and ritonavir pharmacokinetics, blood samples of 5.5 ml were collected by peripheral venous catheter or venipuncture into tubes containing lithium heparin as the anticoagulant, and for the pharmacokinetics of ketoconazole, blood samples of 2.6 ml were collected into EDTA-containing tubes. Plasma was separated by centrifugation for 10 min at 1,500 × *g* and 4°C. The total plasma concentrations of saquinavir and ritonavir were analyzed by PRA International-Early Development Services (formerly Pharma Bio-Research Group B.V, Assen, The Netherlands) using a validated high-pressure liquid chromatography-tandem mass spectrometry method with two linear concentration ranges. The low calibration range was 1.00 to 100 ng/ml for both analytes, using aliquots of 200 μl of plasma. The high calibration range was 10 to 10,000 ng/ml for both analytes, using aliquots of 100 μl of plasma. The precision of the low concentration assay ranged from 0.7 to 7.0% for saquinavir and from 3.6 to 7.8% for ritonavir. The accuracy ranged from 93.1 to 100.2% and from 94.2 to 95.8% for saquinavir and ritonavir, respectively. The precision of the high concentration assay ranged from 3.5 to 6.8% for saquinavir and from 4.2 to 6.4% for ritonavir. The accuracy ranged from 98.9 to 101.4% and from 95.0 to 103.5% for saquinavir and ritonavir, respectively. Total ketoconazole plasma concentrations were analyzed by AAIPharma Deutschland GmbH & Co. KG (formerly AAI Deutschland GmbH & Co. KG, Neu-Ulm, Germany) using a validated high-pressure liquid chromatography-fluorescence method with a calibration range from 25.0 to 2,500 ng/ml, using aliquots of 100 μl of plasma. The precision ranged from 2.2 to 6.0%, and the accuracy ranged from 97.8 to 101.0%.

Pharmacokinetic evaluation. Pharmacokinetic parameters were estimated using standard noncompartmental methods (Software WinNonlin Professional, version 5.2; Pharsight Corp., Mountain View, CA) and actual sampling times. The following pharmacokinetic parameters were directly obtained from the observed concentration-versus-time data: the maximum plasma concentration (C_{max}), the time to C_{max} (T_{max}), and the drug concentration at 12 h after administration (C_{12}) for saquinavir/ritonavir or at 24 h after administration (C_{24}) for ketoconazole. The area under the drug plasma concentration-time curve from time zero until 12 h (AUC_{0-12}) for saquinavir/ritonavir or until 24 h (AUC_{0-24}) for ketoconazole was calculated by applying the linear trapezoidal rule. The terminal elimination half-life ($t_{1/2}$) was estimated by $\ln 2/k_{el}$, where k_{el} is the terminal elimination rate constant determined by linear regression of the last four natural log-transformed concentration time points with a maximum exclusion of one intermediate concentration time point and fitting with an adjusted residuals squared value that is >0.90. The apparent oral plasma clearance at steady state (CL_{ss}/F) was estimated by calculating the dose/AUC_{0-12} for saquinavir and ritonavir and dose/AUC_{0-24} for ketoconazole.

Statistical analysis. In both study arms, predose concentrations measured on the last 2 to 4 days of periods 1 and 2 were summarized per study arm and study day. Pharmacokinetic parameters were summarized per study arm and treatment for all subjects who completed the trial. For the assessment of the drug-drug interaction, the study variables were AUC_{0-12} and C_{max} for saquinavir/ritonavir and AUC_{0-24} and C_{max} for ketoconazole. Natural log-transformed values of these parameters were used, and the exposure ratios were determined in arm 1 for saquinavir and ritonavir for day 28 to day 14 and in arm 2 for ketoconazole for day 20 to day 6. The geometric means of the individual exposure ratios, together with the corresponding two-sided 90% CIs, were calculated. No formal confirmatory hypothesis testing was planned, and P values were interpreted in an exploratory manner. The statistical analysis was performed using software SAS v8.2 (SAS Institute, Inc., Cary, NC).

TABLE 1. Summary of demographic characteristics of the study populations

Characteristic	Study arm 1 ($n = 29$)	Study arm 2 ($n = 13$)
No. of males/no. of females	27/2	13/0
Black/Caucasian	1/28	0/1[a]
Mean age in yr (range)	33.0 (19–62)	30.5 (19–58)
Mean body wt in kg (range)	76.7 (45.0–107.8)	80.4 (64.7–100.0)
Mean body mass index in kg/m^2 (range)	24.5 (18.0–29.5)	25.1 (20.1–29.2)

RESULTS

Demographics. A total of 42 healthy subjects were enrolled in the present study. A total of 29 subjects (27 males and 2 females) were randomly assigned to study arm 1 assessing the effect of ketoconazole on the plasma concentrations of saquinavir/ritonavir, and 13 subjects (all males) were randomly assigned to study arm 2 assessing the effect of saquinavir/ritonavir and the plasma concentrations of ketoconazole. Each of the 42 subjects received at least one dose of study drug(s), and 32 subjects (20 in arm 1, 12 in arm 2) completed the study as planned. The demographic characteristics of the study population are shown in Table 1.

TABLE 2. Geometric mean predose plasma concentrations of saquinavir/ritonavir in study arm 1 ($n = 29$)

Agent	Mean concn (μg/ml)[a]							
	Study arm 1, period 1, at day:				Study arm 1, period 2, at day:			
	11	12	13	14	25	26	27	28
Saquinavir	0.84 (120)	0.97 (71)	0.99 (74)	1.3 (84)	0.67 (90)	0.84 (120)	1.0 (100)	1.3 (66)
Ritonavir	0.29 (130)	0.33 (76)	0.38 (40)	0.38 (74)	0.32 (89)	0.30 (84)	0.40 (75)	0.45 (59)
Ketoconazole					0.93 (44)	1.0 (38)	1.0 (44)	1.1 (36)

[a] The percent CV is indicated in parentheses.

Evaluation of predose concentrations. Serial predose measurements of the last 2 to 4 days of each treatment period are summarized per study arm and treatment day in Tables 2 and 3. In study arm 1, the daily saquinavir and ritonavir predose concentrations were of similar magnitude within each measured period, with pronounced but comparable interindividual variabilities expressed as the %CV in both periods (Table 2). In addition, the daily saquinavir and ritonavir predose concentrations were of similar dimensions in the absence or presence of ketoconazole coadministration. Likewise, in arm 2, the daily ketoconazole predose concentrations were stable within each measured period but were ~17-fold higher in the presence of saquinavir/ritonavir coadministration compared to ketoconazole treatment alone (Table 3). Also, in study arm 2 period 2, the daily saquinavir and ritonavir predose concentrations were not dissimilar from those seen for saquinavir/ritonavir throughout study arm 1.

Assessment of drug-drug interactions. The pharmacokinetic interaction was evaluated in the 20 subjects in arm 1 and the 12 subjects in arm 2, who completed the entire study. Figure 1 shows the 12-h plasma log-transformed concentration-versus-time profiles of saquinavir/ritonavir in the absence (day 14) or presence of ketoconazole coadministration (day 28) in study arm 1, and Fig. 2 shows the respective 24 h profiles of ketoconazole in the absence (day 6) or presence of saquinavir/ritonavir coadministration (day 20) in study arm 2. Summaries of the pharmacokinetic parameters for saquinavir/ritonavir (study arm 1) with or without ketoconazole coadministration are presented in Table 4, and those for ketoconazole with or without saquinavir/ritonavir coadministration are presented in Table 5.

In study arm 1, differences in the plasma concentration-versus-time profiles for saquinavir and ritonavir during coadministration with or without ketoconazole were small and not clinically meaningful. Mean values for all pharmacokinetic parameters of saquinavir and ritonavir were similar in the absence or presence of ketoconazole coadministration, and the interindividual variability (as expressed as the %CV) was similar for both compounds and in both of the treatment periods. The geometric mean ratio estimates for the AUC_{0-12} and C_{max} of saquinavir and ritonavir were close to 1, and all four 90% CIs were within the range of 0.86 to 1.26 (Table 4). Based on these results, it can be concluded that the addition of ketoconazole at a dose of 200 mg once daily to the approved therapeutic regimen of saquinavir/ritonavir at 1,000/100 mg twice daily for 14 days did not have a clinically relevant effect on the pharmacokinetic exposures of saquinavir or ritonavir.

In study arm 2, the plasma concentration-versus-time profiles showed a considerable increase in ketoconazole exposure during coadministration with saquinavir/ritonavir. The terminal elimination of ketoconazole was prolonged after 14 days of coadministration with saquinavir/ritonavir, as indicated by the flatter decline in the log-transformed concentration versus time profile. The absorption of ketoconazole was minimally prolonged during saquinavir/ritonavir coadministration, as expressed by a 1-h delay in the median T_{max} from 2.5 h in period 1 to 3.5 h in period 2. The median $t_{1/2}$ was also prolonged from 4.3 h in period 1 to 10.7 h in period 2, and the geometric mean

TABLE 3. Geometric mean predose plasma concentrations of ketoconazole and saquinavir/ritonavir in study arm 2 ($n = 13$)

Agent	Mean concn (μg/ml)[a]					
	Study arm 2, period 1, at day:		Study arm 2, period 2, at day:			
	5	6	17	18	19	20
Ketoconazole	0.072 (51)	0.070 (60)	1.2 (54)	1.3 (54)	1.2 (47)	1.2 (61)
Saquinavir			1.1 (42)	1.1 (57)	0.83 (62)	1.3 (72)
Ritonavir			0.48 (36)	0.40 (45)	0.42 (70)	0.51 (57)

[a] The percent CV is indicated in parentheses.

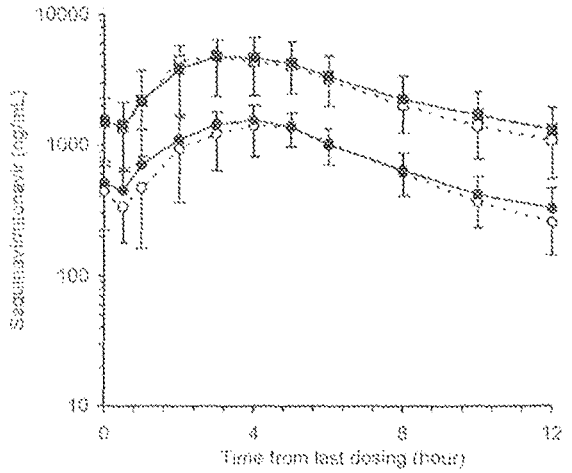

FIG. 1. Mean plasma concentration-time profiles of saquinavir (squares) and ritonavir (circles) after 14 days of saquinavir/ritonavir at 1,000/100 mg given twice daily (open symbols, dotted line) and after 14 days of coadministration of saquinavir/ritonavir with ketoconazole at 200 mg once daily (filled symbols, solid line). The standard deviations are shown as error bars.

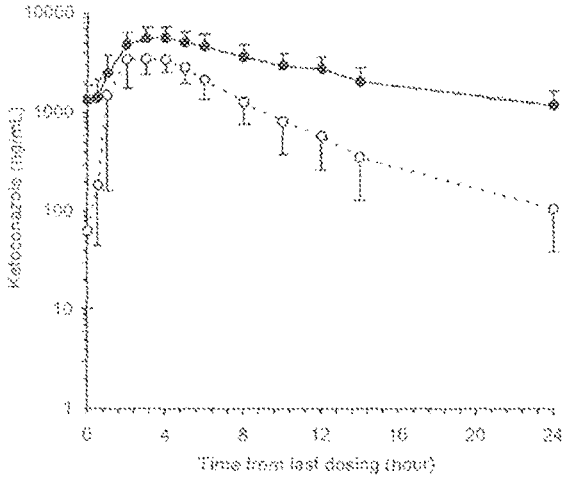

FIG. 2. Mean plasma concentration-time profiles of ketoconazole after 6 days of ketoconazole at 200 mg given once daily (open symbols, dotted line) and after 14 days of coadministration of ketoconazole with saquinavir/ritonavir at 1,000/100 mg twice daily (filled symbols, solid line). The standard deviations are shown as error bars.

CL_{ss}/F value was decreased by more than 50% with saquinavir/ritonavir coadministration, from 8.22 to 3.07 liters/h. Increases in the mean C_{24} values for ketoconazole of >10-fold were seen in period 2 relative to period 1. The intersubject variabilities (as expressed by the %CV) were comparable in periods 1 and 2 for ketoconazole. The geometric mean ratio estimates for AUC_{0-24} and C_{max} of ketoconazole were substantially larger than 1 (Table 5). After 14 days of coadministration of saquinavir/ritonavir, the mean ketoconazole AUC_{0-24} and C_{max} were increased by 2.68- and 1.45-fold, respectively, compared to the administration of ketoconazole alone.

Safety results. The study medications were generally well tolerated by healthy subjects. There were 10 early discontinuations from the study: 9 in study arm 1 and 1 in study arm 2. The reasons for study withdrawals were adverse events in six subjects in arm 1, elevated safety laboratory parameters (high triglycerides and low-density lipoprotein cholesterol, respectively) in two subjects in arm 1, and other reasons in the remaining one subject in arm 1 and the one subject in arm 2. In study arm 1, the adverse events reporting rates were similar in period 1 (days 1 to 14) and period 2 (days 15 to 28), with 62 and 58% of subjects, respectively. Gastrointestinal disorders were the most frequently adverse events reported by 41 and 25% of subjects in periods 1 and 2, respectively, followed by events related to infections and infestations, and nervous system disorders reported by 17% of subjects each during saquinavir/ritonavir treatment in period 1. In study arm 2, the reporting rate for adverse events was lower during period 1 (days 1 to 6) with 23% of subjects compared to that of 92% of subjects in period 2 (days 7 to 20). Again, gastrointestinal disorders were the most prominent adverse events reported by 54% of subjects during triple combination therapy in period 2. The majority of the adverse events were mild to moderate in intensity. All adverse events were resolved without sequelae. The greater exposure to ketoconazole when given in combination with saquinavir/ritonavir was not associated with unacceptable safety or tolerability in the present study.

TABLE 5. Summary of pharmacokinetic parameters for ketoconazole in study arm 2 ($n = 12$)

Parameter	GM (%CV)[a]		GMR (90% CI)[b]
	Period 1 (ketoconazole alone)	Period 2 (ketoconazole + saquinavir + ritonavir)	
C_{max} (μg/ml)	3.86 (28.9)	5.59 (29.1)	1.45 (1.32–1.59)
AUC_{0-24} (μg · h/ml)	24.3 (36.4)	65.2 (32.1)	2.68 (2.46–2.93)
C_{24} (ng/ml)	87.4 (79.7)	1,100 (47.8)	NA
T_{max} (h)	2.5 (2.0–5.0)	3.5 (2.0–4.0)	NA
$t_{1/2}$ (h)	4.3 (2.1–7.0)	10.7 (6.7–18.5)	NA
CL_{ss}/F (liter/h)	8.22 (36.4)	3.07 (32.1)	NA

[a] GM, geometric mean.
[b] GMR, geometric mean ratio of period 2/period 1. NA, not assessed.

DISCUSSION

In order to assess the impact of drug-drug interaction at the CYP3A4 metabolic pathway, strict exclusion criteria were set in the present study with regard to concomitant use of CYP3A4 substrates, inhibitors, or inducers. Since hormonal contraceptives, being CYP3A4 substrates, were not allowed, women had to be of non-child-bearing potential or under efficient nonhormonal contraceptive protection. With these requirements, only two women could be recruited into the

TABLE 4. Summary of pharmacokinetic parameters for saquinavir and ritonavir in study arm 1 ($n = 20$)[a]

Parameter	Saquinavir			Ritonavir		
	GM (%CV)		GMR (90% CI)	GM (%CV)		GMR (90% CI)
	Period 1 (+ ritonavir)	Period 2 (+ ritonavir + ketoconazole)		Period 1 (+ saquinavir)	Period 2 (+ saquinavir + ketoconazole)	
C_{max} (μg/ml)	5.01 (51.5)	5.10 (36.3)	1.02 (0.86–1.20)	1.53 (39.4)	1.66 (26.4)	1.08 (0.96–1.21)
AUC_{0-12} (μg · h/ml)	30.0 (53.3)	32.2 (30.3)	1.07 (0.92–1.26)	8.9 (36.3)	9.95 (30.3)	1.12 (1.03–1.22)
C_{12} (μg/ml)	0.956 (56.3)	1.13 (62.4)	NA	0.230 (57.1)	0.292 (57.7)	NA
T_{max} (h)	3.0 (2.0–6.0)	3.0 (2.0–5.0)	NA	4.0 (2.0–5.0)	4.0 (3.0–5.0)	NA
$t_{1/2}$ (h)	4.9 (4.1–5.9)	5.2 (4.5–6.8)	NA	3.7 (3.1–5.6)	4.2 (3.5–5.5)	NA
CL_{ss}/F (liter/h)	33.4 (53.3)	25.6 (43.3)	NA	11.2 (36.3)	8.7 (32.8)	NA

[a] GMR, geometric mean ratio of period 2/period 1. GM, geometric mean. NA, not assessed.

present study. Both were randomized to study arm 1 and completed all study procedures. Knowing that for saquinavir statistically significant greater exposures have been observed in women than in men (study BP17359 with 87 males and 7 females [Roche data on file]), the exposures of the two women to saquinavir ($AUC_{0,12}$ = 47.7 and 43.4 μg h/ml in period 1 and 29.8 and 66.0 μg h/ml in period 2) in the present study in both periods were similar to those seen in the remaining 18 men within 40 to 53% variability (Table 4), and therefore the conclusions made for the whole population in this study arm may also apply to female patients. On the other hand, the effect of saquinavir and ritonavir on the exposure of ketoconazole (arm 2) was only studied in men. However, lacking data of female subjects in this study arm, and considering also the related safety aspects, it cannot be assumed that this increase in ketoconazole exposure during concomitant saquinavir/ritonavir at a 1,000/100-mg twice-daily treatment would be of different magnitude in women.

In this study in healthy volunteers, the addition of ketoconazole at a dose of 200 mg once daily to the approved therapeutic dosing regimen of saquinavir/ritonavir at 1,000/100 mg twice daily for 2 weeks did not have a clinically relevant effect on the pharmacokinetic exposures of saquinavir and ritonavir. For both compounds, the 90% CIs surrounding the geometric mean ratio estimates for the $AUC_{0,12}$ and C_{max} were within or only 1% exceeding the upper limit of the no-effect boundary (0.80 to 1.25) as defined in the U.S. Food and Drug Administration guideline for the industry for in vivo drug interaction studies (5).

By comparison, after 6 days of pretreatment with ketoconazole at 200 mg once daily, the addition of saquinavir/ritonavir at 1,000/100 mg twice daily for 2 weeks increased the exposure of ketoconazole by 2.68 (2.46 to 2.93)-fold for $AUC_{0,24}$ and by 1.45 (1.32 to 1.59)-fold for C_{max}. The median elimination half-life for ketoconazole was also more than doubled, from 4.3 h after treatment with ketoconazole alone to 10.7 h after coadministration with saquinavir/ritonavir. The reduced clearance of ketoconazole resulted in predose concentrations of ketoconazole that were >10-fold higher in all subjects after coadministration with saquinavir/ritonavir compared to values seen after 6 days of treatment with ketoconazole alone.

The 2-week treatment phases of saquinavir/ritonavir and the concomitant triple-drug treatment with ketoconazole was considered sufficient in order to achieve stable pharmacokinetic conditions for all three medications involved. This treatment duration, although longer than required based on the half-lives of ritonavir and saquinavir, was selected based on the fact that ritonavir not only inhibits the metabolism of CYP3A4 but also increases the enzyme activity of CYP3A4 (inhibition-associated induction). Due to this autoinduction, plasma concentrations of saquinavir/ritonavir generally reach steady state 2 weeks after the start of ritonavir administration (3).

Studies have already been performed investigating the drug-drug interaction between ketoconazole and saquinavir, or ritonavir, or saquinavir/ritonavir using several dosing regimens. In these studies, the saquinavir and ritonavir doses used were different from the approved dosing regimen for saquinavir/ritonavir of 1,000/100 mg twice daily. Coadministration of ketoconazole at 400 mg once daily with saquinavir at 1,200 mg three times daily increased the AUC of saquinavir by 190%, but saquinavir did not change the AUC of ketoconazole (see the product information for Invirase capsules and tablets [Hoffman-La Roche, Inc.]). Coadministration of ritonavir at 500 mg twice daily with ketoconazole at 200 mg once daily resulted in a 3.4-fold increase in the ketoconazole AUC and an 18% increase in ritonavir AUC (see the product information for the Norvir 100-mg capsule [Abbott Laboratories]). Coadministration of saquinavir/ritonavir at 400/400 mg twice daily with ketoconazole at 200 or 400 mg once daily yielded increases in the saquinavir AUC by 37% and the ritonavir AUC by 29% (4). The results of the present study are closest to those obtained with the ritonavir and ketoconazole combination, although the increase in ketoconazole exposure was somewhat less for the AUC in the present study (2.68-fold versus 3.4-fold) and C_{max} (45% in present study versus 55% in the product information for the Norvir 100-mg capsule [Abbott Laboratories]). The metabolism and elimination of ketoconazole are clearly affected by the CYP3A4 inhibitory effect of ritonavir, whereas the influence of ketoconazole, an inhibitor for both CYP3A4 and P-glycoprotein, on the saquinavir/ritonavir combination is small, as shown by the clinically irrelevant increases in plasma exposures of these two compounds. In the present study, the CYP3A4 inhibitory effect of ketoconazole on saquinavir, as seen in the above saquinavir ketoconazole interaction studies, is, for the most part, superimposed by the CYP3A4 inhibitory effect of ritonavir on saquinavir. The increase in the saquinavir AUC by 37% and the ritonavir AUC by 29% when combined with ketoconazole, as observed in an earlier study (4), may have been due to the higher ketoconazole dose (400 mg) and/or different saquinavir/ritonavir doses (400/400 mg) used compared to those in the present study. A full CYP3A inhibitory effect of ketoconazole may not have been reached with the ketoconazole standard dose of 200 mg daily in the present study. However, based on the existing data, and for safety reasons, a ketoconazole multiple-dose regimen of 400 mg daily was not considered acceptable for this study in healthy volunteers due to the hepatic toxicity liability of ketoconazole (see Drug Information Online [http://www.drugs.com/mmx/ketoconazole.html]) and as a result of the maximum 200-mg daily ketoconazole dose recommendations in combination with ritonavir (product information for the Norvir 100-mg capsule [Abbott Laboratories]). With a 400-mg daily dose of ketoconazole in the present study, further increases of ketoconazole plasma concentrations would have been most likely.

The safety results as recorded by adverse events and laboratory safety measurements were consistent with those indicated in the respective product information for these three drugs (see also the product information for the Norvir 100-mg capsule [Abbott Laboratories], for Invirase capsules and tablets [Hoffman-La Roche, Inc.], and for the Nizoral 200-mg tablet [Janssen-Cilag, Ltd.]). There were no vital-sign or ECG abnormalities of clinical relevance recorded during this study.

Conclusions. The present two-arm drug-drug interaction study involving ketoconazole at 200 mg/day and ritonavir-boosted saquinavir (1000 mg of saquinavir and 100 mg of ritonavir twice daily) indicated that the C_{max} and $AUC_{0,12}$ of both saquinavir and ritonavir are not substantially altered by the addition of ketoconazole for the duration of 2 weeks, but that, on the other hand, the C_{max} and $AUC_{0,24}$ of ketoconazole are increased by 45 and 168%, respectively, after the addition

of saquinavir/ritonavir for 2 weeks. The greater exposure to ketoconazole when given in combination with saquinavir/ritonavir was not associated with unacceptable safety or tolerability. It is concluded that no dose adjustment for either saquinavir or ritonavir is required when coadministered with ≤200 mg of ketoconazole once daily and, based on the hepatotoxicity liability of ketoconazole, high doses of ketoconazole (>200 mg/day) are not recommended.

ACKNOWLEDGMENT

We thank the study team members at Hoffman-La Roche for their assistance with the study. All authors are Roche employees.

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EXHIBIT 7

Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome

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Context: Cushing's syndrome (CS) is a disorder associated with significant morbidity and mortality due to prolonged exposure to high cortisol concentrations.

Objective: Our objective was to evaluate the safety and efficacy of mifepristone, a glucocorticoid receptor antagonist, in endogenous CS.

Design and Setting: We conducted a 24-wk multicenter, open-label trial after failed multimodality therapy at 14 U.S. academic medical centers and three private research centers.

Participants: Participants included 50 adults with endogenous CS associated with type 2 diabetes mellitus/impaired glucose tolerance (C-DM) or a diagnosis of hypertension alone (C-HT).

Intervention: Mifepristone was administered at doses of 300-1200 mg daily.

Main Outcome Measures: We evaluated change in area under the curve for glucose on 2-h oral glucose test for C-DM and change in diastolic blood pressure from baseline to wk 24 for C-HT.

Results: In the C-DM cohort, an area under the curve for glucose ($AUC_{glucose}$) response was seen in 60% of patients ($P < 0.0001$). Mean ± SD glycated hemoglobin (HbA1c) decreased from 7.43 ± 1.52% to 6.29 ± 0.99% ($P < 0.001$); fasting plasma glucose decreased from 149.0 ± 75.7 mg/dl (8.3 ± 4.1 mmol/liter) to 104.7 ± 37.5 mg/dl (5.8 ± 2.1 mmol/liter, $P < 0.03$). In C-HT cohort, a diastolic blood pressure response was seen in 38% of patients ($P < 0.05$). Mean weight change was −5.7 ± 7.4% ($P < 0.001$) with waist circumference decrease of −6.78 ± 5.8 cm ($P < 0.001$) in women and −8.44 ± 5.9 cm ($P < 0.001$) in men. Overall, 87% ($P < 0.0001$) had significant improvement in clinical status. Insulin resistance, depression, cognition, and quality of life also improved. Common adverse events were fatigue, nausea, headache, low potassium, arthralgia, vomiting, edema, and endometrial thickening in women.

Conclusions: Mifepristone produced significant clinical and metabolic improvement in patients with CS with an acceptable risk-benefit profile during 6 months of treatment. (***J Clin Endocrinol Metab* 97: 2039–2049, 2012**)

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2011-3350 Received December 12, 2011. Accepted March 8, 2012.
First Published Online March 30, 2012

Abbreviations: AE, Adverse event; AI, adrenal insufficiency; $AUC_{glucose}$, area under the curve for glucose; BDI, Beck Depression Inventory; CD, Cushing's disease; C-DM, patients with CS and T2DM/IGT; C-HT, patients with CS and a diagnosis of HTN; CI, confidence interval; CS, Cushing's syndrome; DBP, diastolic blood pressure; DRB, data review board; ET, early termination; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; HTN, hypertension; IGT, impaired glucose tolerance; mITT, modified intent-to-treat; MRI, magnetic resonance imaging; oGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus.

Cushing's syndrome (CS), is a serious endocrine disorder that may be caused by a pituitary [Cushing's disease (CD)] or nonpituitary (ectopic) ACTH-secreting tumor or by an adrenal neoplasm. If inadequately treated, CS is associated with a 3.8- to 5.0-fold higher mortality than the general population (1–3). Regardless of cause, surgery is usually the treatment of choice; however, complete removal of the neoplasm may not be possible (4, 5). Adjunctive radiotherapy for CD may take years to control excess cortisol (6). Laparoscopic bilateral adrenalectomy represents another treatment option. No medical treatments were approved by the U.S. Food and Drug Administration for CS when the study was conducted, but off-label use of several medications is common, including dopamine agonists, somatostatin analogs, and the adrenal steroidogenesis inhibitors (ketoconazole, metyrapone, mitotane, and etomidate) (4, 7). Ketoconazole and mitotane are effective in many patients, but in CD, doses may need progressive increases due to escape from cortisol blockade. The tolerability of these drugs, especially at higher doses, limits their use in some patients (8, 9).

Mifepristone (11β-[*P*-(dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one) is a progesterone receptor antagonist that has glucocorticoid receptor antagonist activity at higher concentrations, with more than three times the binding affinity for the glucocorticoid receptor than dexamethasone (10, 11). It does not bind to the mineralocorticoid receptor (9). Case reports and small retrospective studies of mifepristone treatment in CS document improvements in abnormal glucose metabolism, psychiatric symptoms, and the somatic changes associated with CS; hypokalemia was the most commonly reported side effect (9, 12–25). Based on these preliminary findings, an open-label, prospective, multicenter, 6-month study of the safety and efficacy of mifepristone was conducted in patients with endogenous CS refractory to other therapies.

Patients and Methods

Patients

Adults with confirmed endogenous CS who had associated type 2 diabetes mellitus (T2DM), impaired glucose tolerance (IGT), or a diagnosis of hypertension (HTN) were enrolled (Fig. 1). Endogenous hypercortisolism was defined as elevated urinary free cortisol on at least two 24-h collections and elevated late-night salivary cortisol and/or lack of suppression with dexamethasone. T2DM was defined as a fasting plasma glucose (FPG) of at least 126 mg/dl ($\geq$7.0 mmol/liter) on two measurements or a 2-h plasma glucose of at least 200 mg/dl ($\geq$11.1 mmol/liter) after a 75-g oral glucose tolerance test (oGTT), and IGT was defined as 2-h oGTT glucose value of 140–199 mg/dl (7.8–11.0 mmol/liter). HTN was defined as systolic blood pressure over 140 mm Hg and/or diastolic blood pressure (DBP) over 90 mm Hg or pharmacologically treated HTN.

At least two of the following signs or symptoms of Cushing's were also necessary for inclusion: Cushingoid appearance (moon facies, dorsocervical fat pad, and plethora), increased body weight or central obesity, proximal muscle weakness, low bone mineral density (T score < -1.0), psychiatric symptoms, and skin changes (hirsutism, violaceous striae, or acne).

Patients were excluded for poorly controlled diabetes mellitus [glycated hemoglobin (HbA1c) $\geq$ 11%], poorly controlled HTN (>170/110 mm Hg), use of drugs to treat hypercortisolism within 1 month of baseline (mitotane for adrenal carcinoma was allowed if on stable dose $\geq$1 month before entry), uncorrected hypokalemia, or uncontrolled hypothyroidism or hyperthyroidism; also excluded were women with a uterus who required anticoagulants or had hemorrhagic disorders, endometrial hyperplasia, carcinoma, or polyps. Increases or additions of antihyperglycemic medications during the study were not permitted for patients with T2DM/IGT. For patients with HTN, increases or additions of antihypertensive medications were not permitted with the exception of mineralocorticoid receptor antagonists, which were allowed for treating hypokalemia, a known side effect of mifepristone (9). Changes in or initiation of antidepressant or lipid-lowering medications were not allowed.

The study was approved by the institutional review board at each center and was registered with www.clinicaltrials.gov (NCT00569582). All patients provided written informed consent.

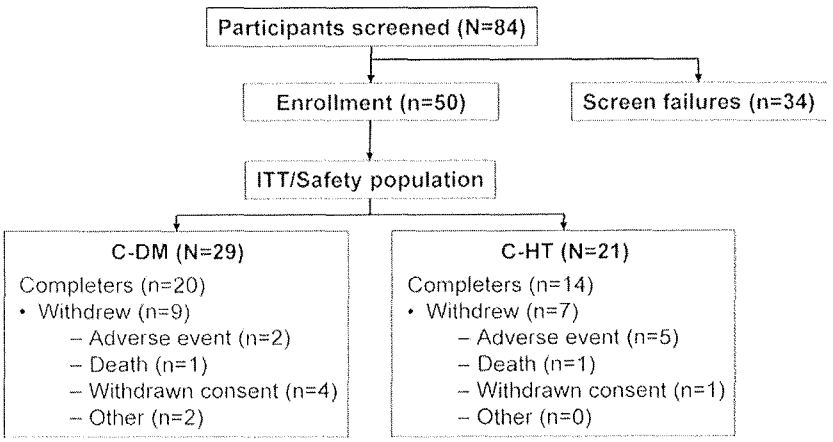

FIG. 1. Enrollment: ITT/safety population.

Design

This was a 24-wk, open-label, multicenter study of mifepristone administered as a single daily oral dose. Treatment began at 300 mg/d; if no significant clinical improvement was noted by the investigator, doses could be increased to 600 mg/d on d 14, 900 mg/d at wk 6, and 1200 mg/d at wk 10. Dose interruption and reduction were specified in the protocol for the following adverse events (AEs): adrenal insufficiency (AI), severe hypokalemia,

and vaginal bleeding. Temporary glucocorticoid rescue for suspected AI was also allowed.

Assessments

The primary endpoint for patients with CS and T2DM/IGT (C-DM cohort) was the change in area under the curve for glucose ($AUC_{glucose}$) on oGTT from baseline to wk 24. Response was defined as at least a 25% decrease in $AUC_{glucose}$, an amount considered clinically meaningful improvement in glucose control (26). $AUC_{glucose}$ was used because both patients with T2DM and patients with IGT were enrolled, and HbA1c and FPG would not be uniformly applicable. In patients receiving medications for diabetes, administration occurred before the oGTT (other than short-acting insulin and glucagon-like peptide-1 analogs). The primary endpoint for patients with CS and a diagnosis of HTN (C-HT cohort) was the change in DBP from baseline to wk 24; response was defined as DBP decrease of at least 5 mm Hg (mean of two sequential readings). Patients with both T2DM/IGT and HTN were included only in the C-DM cohort.

Key secondary endpoints included clinical response graded by an independent data review board (DRB) at wk 6, 10, 16, and 24 compared with baseline. The DRB consisted of three CS experts who evaluated the following assessments: glucose homeostasis, blood pressure, lipids, weight and body composition change, clinical appearance (acne, hirsutism, striae, and Cushingoid appearance) (27, 28) as rated by the investigators, strength, and neuropsychological [Beck Depression Inventory (BDI)-II and Trail Making Test] (29–31) and quality of life [Short-Form 36 Health Survey version 2 (SF-36)] (32) parameters. The DRB also reviewed standardized photographs of 34 consenting patients. Visit number after baseline and mifepristone dose were blinded. Each DRB member categorized patient overall status at follow-up visits as worse (−1), unchanged (0), or having clinically significant improvement (+1) from baseline. If the reviewers' median score was +1, the patient was considered to have clinical improvement.

Blood, urine, and saliva samples were analyzed by a central laboratory (Quest Diagnostics, Collegeville, PA). $AUC_{glucose}$ and $AUC_{insulin}$ were determined using the linear trapezoidal rule; homeostatic model assessment of insulin resistance (HOMA-IR) was calculated (33). Urinary and salivary cortisol levels were assayed with liquid chromatography tandem mass spectrometry [normal ranges, respectively, are 2–42.4 μg/24 h (5.5–117 nmol/24 h) and ≤0.09 μg/dl (2.5 nmol/liter)]; serum cortisol [normal range is 4–22 μg/dl (110–607 nmol/24 h)], and ACTH (normal range is 5–27 pg/ml (1.1–5.9 pmol/liter) for females and 7–50 pg/ml (1.5–11 pmol/liter) for males] were measured with immunochemiluminometric assay.

AEs were reviewed every visit, and patients were monitored with vital signs, physical exams, and blood tests; transvaginal ultrasounds were conducted at baseline, wk 24 [or early termination (ET)], and 6 wks after last dose. Pituitary magnetic resonance imaging (MRI) was performed at screening and at wk 10 and 24 (or ET) in patients with CD. Body composition was measured using dual-energy x-ray absorptiometry at baseline and wk 24 or ET using Hologic (Bedford, MA) or GE Lunar (Madison, WI) instruments; results were submitted to a central reading site for quality control and analysis.

Statistics

Patients who took at least one dose of study medication comprised the safety population (n = 50). A modified intent-to-treat (mITT) population (patients who received ≥30 d of study medication) was used for analyses of efficacy (n = 46). The completer population included participants who completed through wk 24 and were at least 80% compliant with study medication (n = 33).

Because there was no placebo group in this study, a responder analysis was conducted. Responder rates were tested against an *a priori* threshold of 20%, which was chosen based on very low spontaneous response rates in this patient population (<5%) (34). The null hypothesis was to be rejected if the lower bound of the one-sided binomial 95% confidence interval (CI) of responder rates was over 20%. Because mifepristone blocks rather than lowers cortisol, alternative quantitative endpoints (other than cortisol) were assigned at study entry based on inclusion in either C-DM or C-HT cohorts. Two abnormal oGTTs were required for inclusion in the C-DM group; patients with a diagnosis of HTN and without T2DM/IGT were included in the C-HT group. For statistical analysis, response was defined as at least 25% reduction in $AUC_{glucose}$ for C-DM patients or at least 5 mm Hg reduction in DBP in C-HT patients comparing baseline with wk 24/ET. For patients who did not complete the study or have an ET visit, the last available data were used. ANOVA and *t* tests were used for analyses of other endpoints. Nonparametric statistical testing was employed for nonnormally distributed data. Change in oGTT curves over the course of the study was modeled by a hierarchical linear mixed model that took into consideration the correlation within subjects. SAS statistical software versions 9.1.3 and 9.2 (Cary, NC) were used. Data are shown as mean ± SD unless otherwise stated.

Results

Patients

From January 2008 to January 2011, 50 patients with CS were enrolled at 17 U.S. centers; 34 completed the study. Forty-three patients had a pituitary source of CS (42 with unsuccessful pituitary surgery, 18 with pituitary radiation, and one without previous surgery), four had ectopic ACTH secretion, and three had adrenal cortical carcinoma. Baseline characteristics are detailed in Tables 1 and 2. The mean dose ± SD at the final study visit was 732 ± 366 mg/d. Twenty-two subjects received the maximum dose of 1200 mg/d. Dose interruptions occurred in 42% of patients with median duration of 2 d (range 1–39 d). There were 18 dose reductions in 12 patients; reductions occurred most commonly in 300-mg decrements (317 ± 114 mg).

Primary efficacy analyses

Patients with T2DM/IGT

In the C-DM mITT population, $AUC_{glucose}$ decreased by at least 25% on oGTT in 15 of 25 (60%) patients from baseline to wk 24/ET (95% CI lower bound 42%, $P < 0.0001$) with a median decrease of 36% [30330.0 mg/dl·120 min (1683.3 mmol/liter·120 min) to 20655.0 mg/dl·120 min (1146.4 mmol/liter·120 min)] as well as comparable reductions in plasma glucose levels (Fig. 2 and

TABLE 1. Demographics and body measurements at baseline (ITT/safety population)

Characteristic	C-DM (n = 29)	C-HT (n = 21)	Overall (n = 50)
Sex [n (%)]			
Male	7 (24.1)	8 (38.1)	15 (30.0)
Female	22 (75.9)	13 (61.9)	35 (70.0)
Race [n (%)]			
Black or African-American	6 (20.7)	2 (9.5)	8 (16.0)
White	23 (79.3)	19 (90.5)	42 (84.0)
Ethnicity [n (%)]			
Hispanic or Latino	2 (6.9)	2 (9.5)	4 (8.0)
Not Hispanic or Latino	27 (93.1)	19 (90.5)	46 (92.0)
Age (yr)			
Mean ± SD	44.4 ± 13.71	46.7 ± 8.83	45.4 ± 11.85
Median	41.0	46.0	45.0
Range	26–71	26–67	26–71
Height (cm)			
Mean ± SD	168 ± 12.11	166 ± 8.84	167 ± 10.81
Median	168	163	166
Range	143.5–190.5	154.0–185.4	143.5–190.5
Weight (kg)			
Mean ± SD	105 (33.54)	91.4 (21.10)	99.5 (29.55)
Median	102	88.2	92.4
Range	61.3–198.7	62.7–150.5	61.3–198.7
BMI (kg/m^2)			
Mean ± SD	37.4 (11.18)	33.4 (7.44)	35.7 (9.90)
Median	35.1	31.8	33.5
Range	24.1–66.4	24.5–53.6	24.1–66.4
Waist circumference, cm			
Mean ± SD	124 (21.73)	111 (15.77)	119 (20.31)
Median	120	104	115
Range	97.9–178.4	88.5–153.5	88.5–178.4
Etiology of CS			
CD [n (%)]	24 (82.8)	19 (90.5)	43 (86.0)
Ectopic ACTH [n (%)]	3 (10.3)	1 (4.8)	4 (8.0)
Adrenal cancer [n (%)]	2 (6.9)	1 (4.8)	3 (6.0)

The C-DM group included subjects with T2DM and/or IGT at screening and d 1 as determined by two or more abnormal oGTT. The C-HT group included subjects with a diagnosis of HTN at screening but without T2DM and/or IGT.

Table 3). Similar reductions in $AUC_{glucose}$ were observed in the C-DM ITT and completer populations. The most common doses among responders at wk 24/ET were 600 mg (40%) and 1200 mg (40%), followed by 300 mg (13.3%) and 900 mg (6.7%). In exploratory analyses we found no relationship between the incremental change in dose from baseline and $AUC_{glucose}$ (see Supplemental Fig. 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

Patients with HTN

In the C-HT mITT cohort, eight of 21) patients (38.1% achieved the primary endpoint of at least 5 mm Hg decline in DBP (95% CI lower bound 21%, $P < 0.05$; Table 3). Four patients (two responders) received spironolactone during the study; one nonresponder was on spironolactone at entry and remained on a stable dose throughout the study.

Secondary endpoints

Clinical improvement

The overall clinical improvement response rate as assessed by the DRB in the mITT population was 87% (95% CI lower bound 76%, $P < 0.0001$); response rates were similar in the C-DM and C-HT cohorts (Table 3). Thirty-three patients

TABLE 2. Biochemistry at baseline (ITT/safety population)

	CD	Ectopic ACTH	Adrenal cancer	Overall
Biochemistry				
ACTH (pg/ml)	63 (51)	153 (140.3)		66 (66)
24 h UFC (μg/24 h)	139 (137)	2471 (3266)	812 (559)	366 (1049)
Serum cortisol (μg/dl)	21.2 (6.0)	42.6 (14.3)	37.4 (15.4)	23.9 (10.0)
Late-night salivary cortisol (μg/dl)	0.29 (0.29)	1.90 (2.26)	1.02 (0.58)	0.47 (0.83)

To convert values of ACTH to picomoles per liter, multiply by 0.22; urinary free cortisol (UFC) to nanomoles per 24 h, multiply by 2.759; cortisol to nanomoles per liter, multiply by 27.59.

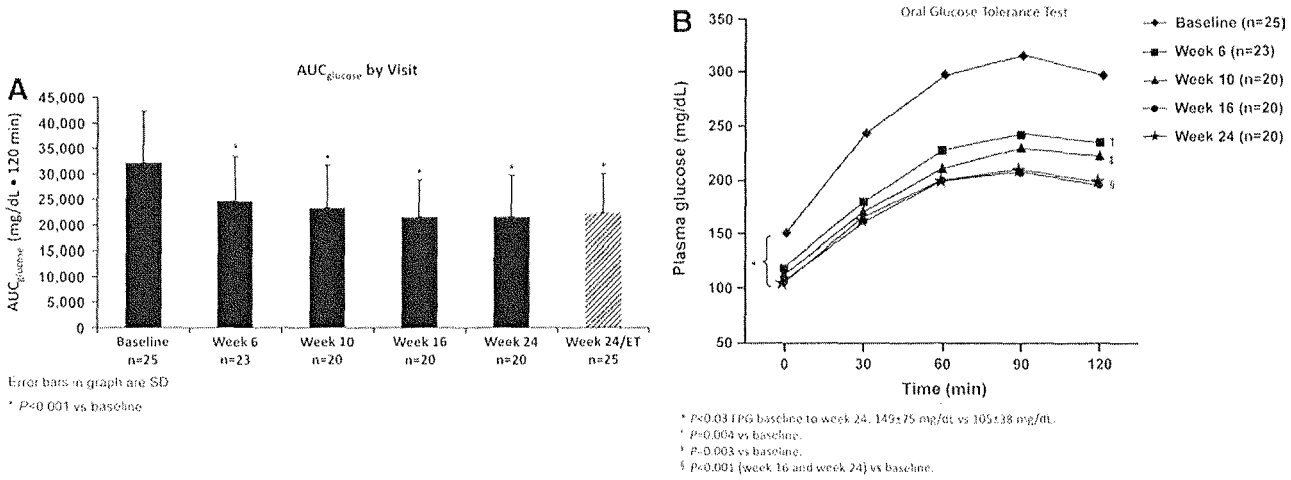

FIG. 2. Changes in glycemic parameters. A, Significant decreases in $AUC_{glucose}$ were observed in the C-DM cohort from baseline to each subsequent visit including wk 24/ET ($P < 0.001$). Data are shown as mean ± SD. B, Significant decreases were also seen in plasma and fasting plasma glucose ($P = 0.03$), as measured by oGTT from baseline to wk 24. The oGTT response curves at each visit were statistically different compared with baseline. Mean data are shown. To convert glucose values to millimoles per liter, multiply by 0.0555.

(72%) had a median score of +1 at wk 24 or ET. Eleven patients by wk 6 and another six patients by wk 10 had a median score of +1 with responses maintained throughout the remainder of the study (Initial clinical improvement response by dose and visit are shown in Supplemental Fig. 2). Three patients had a nonsustained improvement (median score of +1 decreased to 0 at wk 24 or ET). One patient was rated as being worse at the final visit (early termination at wk 10) than at baseline.

Other glucose-related endpoints

FPG decreased from 149.0 ± 74.7 mg/dl (8.3 ± 4.1 mmol/liter) at baseline to 104.7 ± 37.5 mg/dl (5.8 ± 2.1 mmol/liter) at wk 24 ($P < 0.03$). Antidiabetic medications were reduced in seven of 15 patients. Of 12 patients taking insulin, five reduced their daily dose by at least half. Eighteen of 25 C-DM patients (72%) had at least a 25% reduction from baseline in $AUC_{glucose}$ or a reduction in antidiabetic medication (95% CI = 50.6–

TABLE 3. Summary of responder analyses (mITT population)

Statistics (mITT population)	Responder [n (%)]	Nonresponder [n (%)]	Lower bound one-sided 95% exact binomial CI (%)	*P* value
C-DM (n = 25)				
Participants with or without a 25% reduction from baseline in $AUC_{glucose}$ at wk 24/ET	15 (60)	10 (40)	41.7	<0.0001
C-HT (n = 21)				
Participants who had ≥5 mm Hg reduction from baseline in DBP at wk 24/ET	8 (38.1)	13 (61.9)	20.6	<0.05
C-HT and C-DM with HTN at screening (n = 40)				
Participants who had ≥5 mm Hg reduction from baseline in DBP at wk 24/ET	17 (42.5)	23 (57.5)		
Participants who had a reduction in antihypertensive medications at wk 24/ET	11 (27.5)	29 (72.5)		
Participants who had either ≥5 mm Hg reduction from baseline in DBP or had a reduction in antihypertensive medications at wk 24/ET	21 (52.5)[a]	19 (47.5)		
Median clinical improvement score of +1 at any reviewed visit[b]				
Combined cohorts (n = 46)	40 (87.0)	6 (13.0)	75.9	<0.0001
C-DM (n = 25)	23 (92.0)	2 (8.0)	76.9	
C-HT (n = 21)	17 (81.0)	4 (19.0)	61.6	

[a] 95% CI = 36.1–68.5.

[b] For overall clinical improvement (median DRB score +1) at any reviewed visit, the null hypothesis was to be rejected in favor of the alternative if the lower limit of the 95% exact one-sided binomial CI for the responder rate was at least 30%.

87.9%). The mean baseline HbA1c of 7.43 ± 1.52% in the C-DM group decreased to 6.29 ± 0.99% at wk 24/ET ($P < 0.001$) (Fig. 3A). Twelve C-DM patients had an HbA1c over 7% at baseline (mean 8.53 ± 1.11%); of these, nine achieved an HbA1c below 7%, including six reaching an HbA1c of 6% or below. C-DM and C-HT patients were insulin resistant and demonstrated rapid and significant improvements in $AUC_{insulin}$, which continued throughout the study (Fig. 3B); HOMA-IR demonstrated improvements in insulin sensitivity (Fig. 3C).

Weight and body composition

In the mITT population (n = 46), mean ± SD body weight change from baseline (99.5 kg) to wk 24/ET was −5.7 ± 7.4% ($P < 0.001$) (Fig. 4A). Twenty-four patients lost at least 5% of their baseline weight, 12 of whom lost at least 10%; 10 patients gained an average of 3.6 ± 3.9%. Waist circumference decreased by −6.8 ± 5.8 cm ($P < 0.001$) in women and −8.4 ± 5.9 cm in men ($P < 0.001$) (Fig. 4B). Mean percent total body fat declined by 3.6% by wk 24 ($P < 0.001$). Absolute fat mass declined by 13.9% ($P < 0.001$) for the total body, 15.6% ($P < 0.001$) for the trunk, and 17.1% ($P < 0.001$) for the abdominal region (Fig. 4C).

DBP and antihypertensive medications (C-HT and C-DM with HTN)

In addition to the 21 C-HT patients, 19 C-DM patients had a diagnosis of HTN at study entry; 42.5% (17 of 40) of these had a reduction in DBP of at least 5 mm Hg at wk 24/ET compared with baseline, and 27.5% had reductions in antihypertensive medications (50% of patients with a diagnosis of HTN were taking at least two antihyperten-

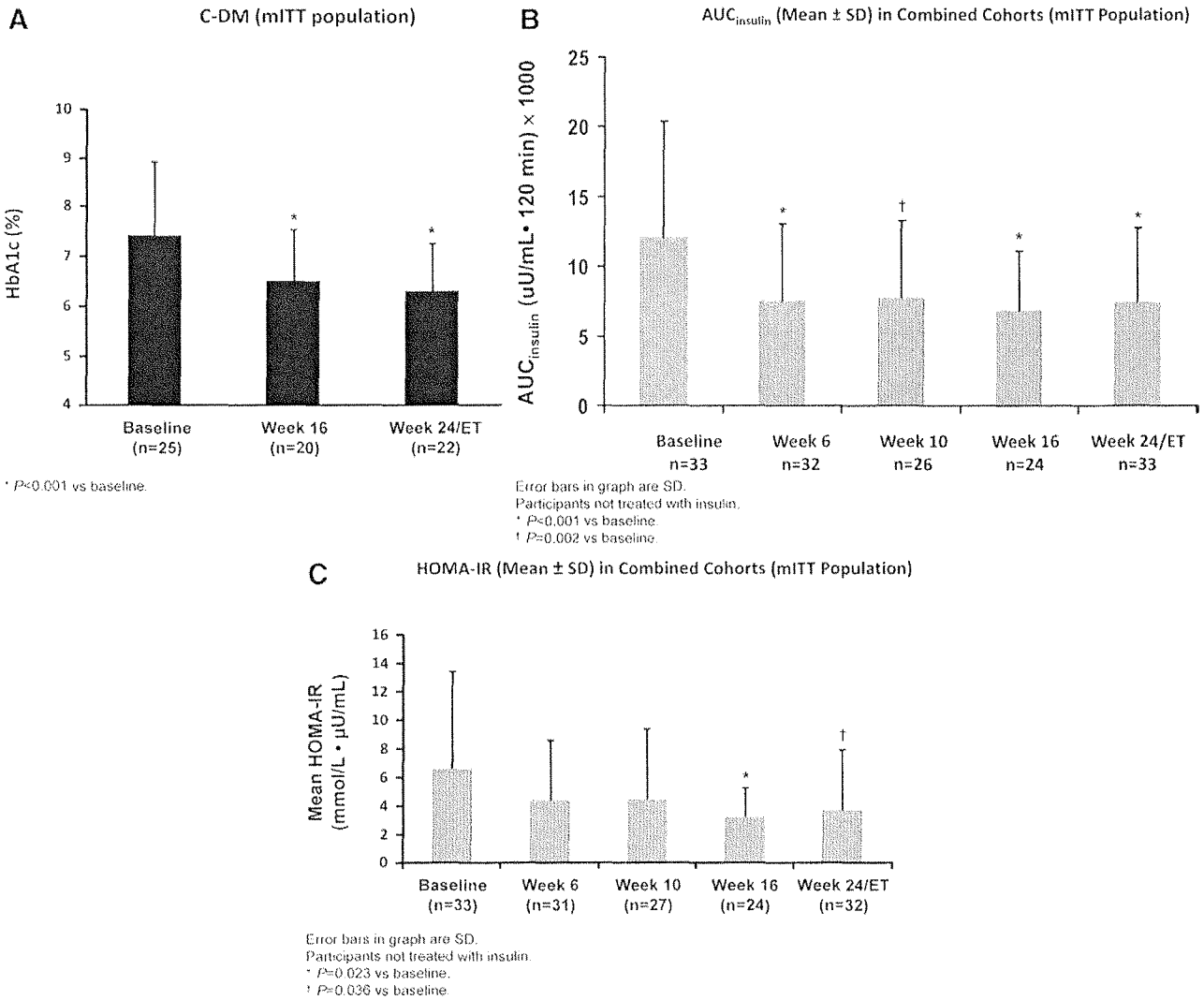

FIG. 3. Changes in glucose-related outcomes. A, HbA1c significantly decreased from baseline to wk 24/ET ($P < 0.001$); B and C, a significant reduction in $AUC_{insulin}$ (B) and significant improvements in HOMA-IR (C) were also observed. Data are shown as mean ± SD. To convert insulin values to picomoles per liter, multiply by 6.945.

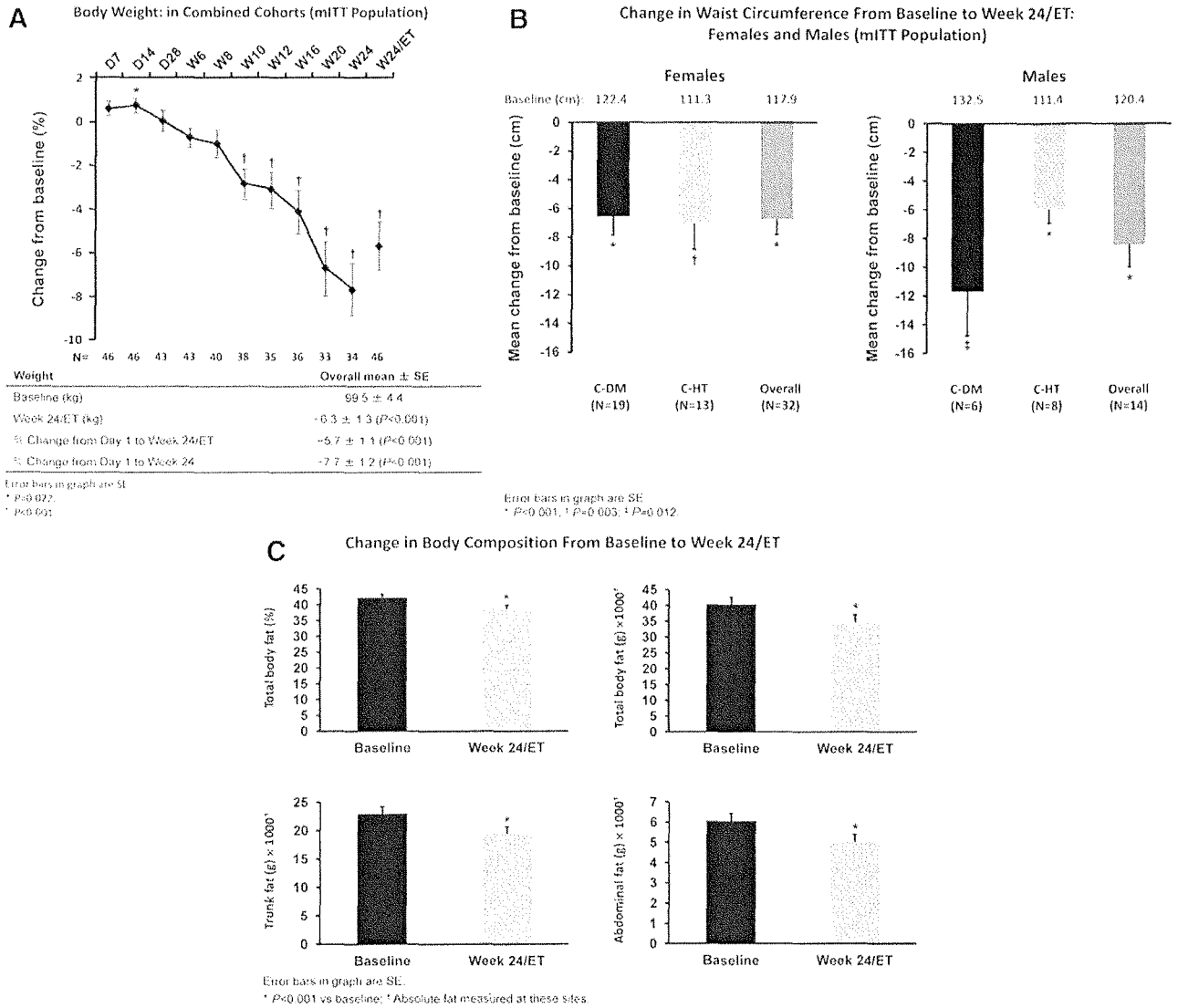

FIG. 4. Changes in weight and body composition. Results demonstrated a significant reduction in body weight from baseline to wk 24/ET ($P < 0.001$) (A), significant decreases in overall waist circumference for females and males ($P < 0.001$) (B), and improvements in body composition (C). Data are shown as mean ± SE.

sive medications at baseline). Overall, 52.5% (95% CI = 36.13–68.49%) had either a response in DBP or a reduction in antihypertensive medications (Table 3). However, there were no significant differences in mean systolic blood pressure and DBP from baseline to wk 24/ET among C-HT patients (129.5 ± 16.3/82.9 ± 11.4 *vs.* 129.9 ± 19.0/82.8 ± 13.2 mm Hg) or in C-DM patients with a diagnosis of HTN (137.7 ± 24.0/86.4 ± 15.3 *vs.* 132.2 ± 16.7/82.4 ± 13.2 mm Hg). Eight of 12 patients with DBP of at least 90 mm Hg at study entry had a reduction of at least 5 mm Hg (median decline −14 mm Hg, range −26.5 to −5.5 mm Hg); only one (C-DM patient) of the eight received additional antihypertensive therapy. AEs of increased blood pressure were reported in 12 patients, nine (75%) of whom had evidence of mineralocorticoid receptor activation (edema, hypokalemia, and/or need for spironolactone to control hypokalemia).

Mood, cognition, and quality of life

Median BDI-II depression scores improved in the mITT population (baseline 14.5, range 0–49; wk 24/ET 9.5, range 0–36; $P < 0.001$). For patients with at least mild depression at baseline (BDI-II ≥ 14, n = 24), median BDI-II scores improved from 23 (range 14–49) to 12 (range 0–34) ($P < 0.001$). Cognition scores were measured by the Trail Making Test at wk 24/ET; there were improvements in both Trail A (median decrease of 4.0 sec, $P < 0.01$) and Trail B (median decrease of 12 sec, $P < 0.01$). Quality of life improved at wk 24/ET as measured by SF-36 mental composite scores (mean 40.0 ± 14.5 *vs.*

45.4 ± 12.5, $P = 0.01$) and physical composite scores (mean 34.9 ± 11.0 *vs.* 39.1 ± 10.8, $P = 0.02$).

Hormone and pituitary MRI scan changes

During mifepristone treatment, 72% of the 43 patients with CD had at least a 2-fold increase in ACTH, cortisol, or both; 28% had smaller increases. These changes were observed early (by d 14), plateaued from wk 10–24, and declined to baseline levels at the follow-up visit 6 wk after discontinuation of mifepristone. Increases in ACTH of at least 2-fold were observed in 62.8% of patients; 33.6% had lesser increases, and 4.7% had no change. Late-night salivary cortisol increased 7.92-fold (1.43) at wk 16, and urinary free cortisol increased 7.70-fold (15.29) at wk 24/ET. At the 6-wk follow-up visit, ACTH and cortisol (serum and urine) declined to near baseline levels. Patients with ectopic ACTH secretion did not demonstrate increases in ACTH and cortisol in response to mifepristone.

Pituitary MRIs were obtained in 41 CD patients; 17 had visible tumors, 10 of which were macroadenomas, and the remaining 24 did not have demonstrable tumors after surgery. MRIs were stable at wk 10 and 24 in all cases except one. This patient had an aggressive pituitary tumor at baseline that was increased in size at wk 10, leading to treatment discontinuation.

Safety

Overall, AEs were reported in 88% of patients during mifepristone treatment, most commonly nausea (48%), fatigue (48%), headache (44%), decreased blood potassium (34%), arthralgia (30%), vomiting (26%), peripheral edema (26%), HTN (24%), dizziness (22%), decreased appetite (20%), and endometrial thickening (20%). The majority of AEs were considered mild or moderate. Seven patients discontinued mifepristone because of an AE; fatigue was the only cause of discontinuation for more than one patient (n = 2). Interruptions or reductions in mifepristone due to AEs, most commonly nausea (n = 6), occurred in 40% of patients; there were interruptions or reductions for protocol-specified events in four subjects (two for AI, one for severe hypokalemia, and one for vaginal bleeding). After dose interruption or reduction before wk 10, there were increases in dose in one of four and two of five patients, respectively; after wk 10, dose escalation did not occur after an interruption for an AE except in a single patient. Four patients experienced progression of preexisting metastatic malignancy that resulted in death.

AI was reported in two patients. One occurred during an infection and responded to withdrawal of mifepristone; the other resolved with mifepristone withdrawal and dexamethasone administration (6–9 mg by mouth daily for 6 d). Neither episode was associated with hypoglycemia or hypotension, and mifepristone was restarted at a lower dose. Analysis of AEs and concomitant medications identified five other instances of two or more symptoms possibly consistent with AI during which glucocorticoids were administered. Dexamethasone doses for these episodes ranged from 2–8 mg daily in tapering amounts for 1–12 d. Vaginal bleeding was observed during the study in five premenopausal women. Prolonged metrorrhagia was observed in two of them after discontinuing mifepristone. Endometrial thickening was reported as an AE in 10 women. Three women underwent dilatation and curettage for unresolved endometrial thickening.

Twenty-two patients had a serum potassium level less than 3.5 mEq/liter (<3.5 mmol/liter), but only three experienced severe hypokalemia [≤2.5 mEq/liter (≤2.5 mmol/liter)] during mifepristone treatment, including one serious AE [potassium 2.1 mEq/liter (2.1 mmol/liter)]. Hypokalemia occurred in patients with both ACTH-dependent and independent CS. Four (one adrenal cancer and three ectopic ACTH) of seven patients with nonpituitary CS experienced hypokalemia during treatment. Hypokalemia was often associated with alkalosis and edema and generally responded to potassium replacement (10–420 mEq daily); all nonpituitary CS patients received potassium supplementation. Overall, spironolactone (50–400 mg daily) was used by 14 patients; it was started or increased in 11 patients for hypokalemia while taking mifepristone, including one patient with adrenal cancer and two patients with ectopic ACTH secretion. Reversible decreases in high-density lipoprotein cholesterol (HDL-C) and increases in TSH were observed. The mean change in HDL-C from baseline [62.3 ± 27.8 mg/dl (1.61 ± 0.72 mmol/liter)] to wk 24/ET was −14.2 ± 11.9 mg/dl (0.37 ± 0.31 mmol/liter) ($P < 0.001$); there were small declines in low-density lipoprotein cholesterol and triglycerides that were not statistically significant. Eight patients had undetectable TSH at baseline; of the remaining 42 patients, eight had increases in TSH above normal (three with TSH > 10 μU/liter, one with TSH of 32 μU/liter). Six weeks after mifepristone discontinuation, both HDL-C and thyroid function tests reverted to baseline levels.

Discussion

Cushing's syndrome is a complex endocrine condition with serious sequelae, including cardiovascular mortality, fractures, proximal myopathy, insulin-resistant hyperglycemia, and neuropsychiatric and neurocognitive disorders (35, 36). Transsphenoidal pituitary surgery with adenoma resection is initially successful in 65–90% of patients with ACTH-secreting microadenomas when performed by ex-

pert surgeons, but approximately 20–25% have persistent hypercortisolism or recurrence postoperatively; cure rates are lower and recurrence rates are higher for macroadenomas (4). Morbidity and mortality in patients with CD are related to cortisol excess and rarely to the ACTH-secreting pituitary tumor mass. When surgery fails to reverse hypercortisolemia, medical treatment can suppress cortisol overproduction and improve clinical manifestations. Bilateral adrenalectomy promptly resolves hypercortisolism but causes permanent adrenal cortical insufficiency mandating lifelong corticosteroid and mineralocorticoid replacement therapy. It may also decrease quality of life (5, 37) and can result in an enlargement of an ACTH-secreting pituitary tumor in 15–20% of cases (38). Patients with ectopic ACTH-secreting neoplasms or adrenocortical carcinoma often require control of hypercortisolism while waiting for definitive therapy or if definitive therapy is not feasible (39).

Mifepristone, a glucocorticoid receptor antagonist with binding affinity greater than dexamethasone and cortisol (10, 11), is rapidly absorbed orally, highly protein bound, and has a long half-life (40). The use of mifepristone in CS has been explored in case reports and/or small retrospective studies (9, 12–25). This is the largest prospective multicenter trial of mifepristone and demonstrates effectiveness in treating the clinical and metabolic derangements associated with hypercortisolism.

The two primary study endpoints were met: mifepristone significantly decreased $AUC_{glucose}$ during oGTT in patients with CS and T2DM or IGT and decreased DBP in a significant number of patients with CS and HTN. Significant decreases in FPG and HbA1c occurred in the C-DM cohort, and more than half the hypertensive patients in both groups had either an improvement in DBP or a reduction in antihypertensive medication. However, overall, there was no change in mean blood pressure from baseline to end of study.

As expected with a receptor-blocking strategy, ACTH and cortisol levels increased in patients with CD. Because high cortisol may not be completely inactivated by 11β-hydroxysteroid dehydrogenase type 2 in the kidney, excess cortisol may activate the mineralocorticoid receptor (41). This likely explains the increased blood pressure, hypokalemia, edema, and alkalosis seen in some patients; nine of the 12 patients with increased blood pressure were prescribed spironolactone.

Secondary endpoint results were noteworthy: mifepristone significantly decreased body weight, waist circumference, and body fat and increased insulin sensitivity. Clinically significant improvement was seen in 87% of patients, according to well-defined criteria used by the DRB. Moreover, 30 of the 34 patients who completed the 24-wk study elected to continue treatment with mifepristone.

Weight loss observed in the study may have been partially due to commonly experienced nausea and decreased appetite (see Supplemental Fig. 3) as well as to a direct result of glucocorticoid blockade. Moreover, it is not possible to discern whether these AEs result from medication or secondarily through a therapeutic effect of glucocorticoid withdrawal. Although clinically significant AI is a potential side effect of glucocorticoid receptor antagonism (9), it was uncommon during this study. Only two patients were reported to have AI; possible symptoms of AI including anorexia, nausea, lethargy, and dizziness occurred in five additional patients who also received glucocorticoids. It is important to note that cortisol elevations that occur in CD could be misleading and render the diagnosis of AI difficult. Without any available biochemical marker, these patients require close monitoring during treatment.

Decreased HDL-C and increased TSH were observed in some patients; these abnormalities resolved upon discontinuation of mifepristone. Because of its antiprogesterone effects, mifepristone has an impact on the endometrium characterized by thickening, with cystically dilated endometrial glands and features usually seen separately in normal proliferative and secretory endometrium (42). Ten women had AE of endometrial thickening, and abnormal vaginal bleeding occurred in five patients. An ongoing, long-term extension study will further characterize the safety profile of mifepristone in CS.

With the exception of a very aggressive tumor in one patient, there were no increases in tumor size, but it is important to note that the study duration was only 6 months. Data from longer-term use of mifepristone will be required to determine whether this risk is similar to that after bilateral adrenalectomy (38).

Limitations of the study include the lack of a placebo comparator group, the open-label design, exclusion of patients with *de novo* Cushing's who were candidates for surgery, and the small number of adrenal cancer and ectopic ACTH cases. The dosing scheme allowing investigators to use their clinical judgment regarding increasing mifepristone based on benefit *vs.* tolerance produced heterogeneity in management, which is a limitation of the study. Similarly, interruptions or reduction in the dose of mifepristone to manage AE produced additional dosing pattern heterogeneity. An assessment of dose response overall was therefore not possible.

Glucocorticoid receptor antagonism with mifepristone may offer a new approach to control the clinical manifestations of endogenous hypercortisolism in patients who have not responded to multimodal therapies. Although the side effect profile over 6 months is well characterized and

manageable with additional medications, the long-term efficacy and safety remain to be determined, particularly with regard to the need for potassium supplementation and/or mineralocorticoid receptor blockade and endometrial monitoring. Because mifepristone does not decrease cortisol production, measurement of this hormone should not be performed during treatment; careful monitoring by clinicians familiar with the mechanism of action of this unique agent is essential. Long-term data are needed to further define the role of mifepristone in the medical treatment of CS.

Acknowledgments

The SEISMIC Study Investigators include Richard Auchus, University of Texas Southwestern Medical Center, Dallas, TX; Timothy Bailey, AMCR Institute Inc., Escondido, CA; Beverly M. K. Biller, Massachusetts General Hospital, Harvard Medical School, Boston, MA; Ty Carroll, Medical College of Wisconsin, Milwaukee, WI; Kathleen Colleran, University of New Mexico Health Sciences Center, Albuquerque, NM; Henry Fein, Sinai Hospital of Baltimore, Baltimore, MD; James W. Findling, Medical College of Wisconsin, Milwaukee, WI; Maria Fleseriu, Oregon Health & Science University, Portland, OR; Amir Hamrahian, Cleveland Clinic Foundation, Cleveland, OH; Laurence Katznelson, Stanford University Medical Center, Stanford, CA; Janice Kerr, University of Colorado Health Science Center at Fitzsimon, Aurora, CO; Mark Kipnes, Cetero Research/Diabetes and Glandular Disease Research, San Antonio, TX; Lawrence Kirschner, Ohio State University Medical Center, Columbus, OH; Christian Koch, University of Mississippi Medical Center, Jackson, MS; Sam Lerman, The Center for Diabetes and Endocrine Care, Hollywood, FL; Timothy Lyons, Oklahoma University Health Science Center, Oklahoma City, OK; Michael McPhaul, University of Texas Southwestern Medical Center, Dallas, TX; Mark E. Molitch, Northwestern University Feinberg Medical, Chicago, IL; David E. Schteingart, University of Michigan Medical Center, Ann Arbor, MI; T. Brooks Vaughan III, University of Alabama at Birmingham School of Medicine, Birmingham, AL; and Roy Weiss, The University of Chicago, Chicago, IL.

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This study was supported by Corcept Therapeutics.

All drafts of the manuscript were written and reviewed by all the authors.

Disclosure Summary: B.M.K.B., J.W.F., and M.E.M. are consultants to Corcept Therapeutics, Inc. B.M.K.B., J.W.F., M.E.M., M.F., and D.E.S. served as investigators on research grants to their institutions from Corcept Therapeutics, Inc. C.G. is an employee of Corcept Therapeutics, Inc. B.M.K.B., J.W.F., and M.F. are consultants to and serve as investigators on research grants to their institutions from Novartis.

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EXHIBIT 8

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KORLYM® safely and effectively. See full prescribing information for KORLYM®.

KORLYM® (mifepristone) 300 mg Tablets

Initial U.S. Approval 2000

WARNING: TERMINATION OF PREGNANCY

See full prescribing information for complete boxed warning.

Mifepristone has potent antiprogestational effects and will result in the termination of pregnancy. Pregnancy must therefore be excluded before the initiation of treatment with KORLYM, or if treatment is interrupted for more than 14 days in females of reproductive potential.

RECENT MAJOR CHANGES

Dosage and Administration (2.1)	05/2017
Warnings and Precautions (5.6)	05/2017

INDICATIONS AND USAGE

KORLYM (mifepristone) is a cortisol receptor blocker indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery (1).

- **Important Limitations of Use:** Do not use for the treatment of type 2 diabetes mellitus unrelated to endogenous Cushing's syndrome.

DOSAGE AND ADMINISTRATION

- Administer once daily orally with a meal (2.1).
- The recommended starting dose is 300 mg once daily (2.1).
- Based on clinical response and tolerability, the dose may be increased in 300 mg increments to a maximum of 1200 mg once daily. Do not exceed 20 mg/kg per day (2.1).
- Renal impairment: do not exceed 600 mg once daily (2.2).
- Mild-to-moderate hepatic impairment: do not exceed 600 mg once daily. Do not use in severe hepatic impairment (2.3).
- Concomitant administration with strong CYP3A inhibitors: Do not exceed 600 mg once daily (2.4).

DOSAGE FORMS AND STRENGTHS

Tablets: 300 mg (3)

CONTRAINDICATIONS

- Pregnancy (4.1, 8.1)
- Use of simvastatin or lovastatin and CYP3A substrates with narrow therapeutic range (4.2)
- Concurrent long-term corticosteroid use (4.3)
- Women with history of unexplained vaginal bleeding (4.4)
- Women with endometrial hyperplasia with atypia or endometrial carcinoma (4.4)

WARNINGS AND PRECAUTIONS

- *Adrenal insufficiency*: Patients should be closely monitored for signs and symptoms of adrenal insufficiency (5.1).
- *Hypokalemia*: Hypokalemia should be corrected prior to treatment and monitored for during treatment (5.2).
- *Vaginal bleeding and endometrial changes*: Women may experience endometrial thickening or unexpected vaginal bleeding. Use with caution if patient also has a hemorrhagic disorder or is on anti-coagulant therapy (5.3).
- *QT interval prolongation*: Avoid use with QT interval-prolonging drugs, or in patients with potassium channel variants resulting in a long QT interval (5.4).
- *Use of Strong CYP3A Inhibitors:* Concomitant use can increase mifepristone plasma levels. Use only when necessary and limit mifepristone dose to 600 mg (5.6).

ADVERSE REACTIONS

Most common adverse reactions in Cushing's syndrome (≥ 20%): nausea, fatigue, headache, decreased blood potassium, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite, endometrial hypertrophy (6).

To report suspected adverse reactions, contact Corcept Therapeutics at 1-855-844-3270 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Drugs metabolized by CYP3A: Administer drugs that are metabolized by CYP3A at the lowest dose when used with KORLYM (7.1).
- CYP3A inhibitors: Caution should be used when KORLYM is used with strong CYP3A inhibitors. Limit mifepristone dose to 600 mg per day when used with strong CYP3A inhibitors (7.2).
- CYP3A inducers: Do not use KORLYM with CYP3A inducers (7.3).
- Drugs metabolized by CYP2C8/2C9: Use the lowest dose of CYP2C8/2C9 substrates when used with KORLYM (7.4).
- Drugs metabolized by CYP2B6: Use of KORLYM should be done with caution with bupropion and efavirenz (7.5).
- Hormonal contraceptives: Do not use with KORLYM (7.6).

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Discontinue drug or discontinue nursing (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: TERMINATION OF PREGNANCY

Mifepristone is a potent antagonist of progesterone and cortisol via the progesterone and glucocorticoid (GR-II) receptors, respectively. The antiprogestational effects will result in the termination of pregnancy. Pregnancy must therefore be excluded before the initiation of treatment with KORLYM and prevented during treatment and for one month after stopping treatment by the use of a non-hormonal medically acceptable method of contraception unless the patient has had a surgical sterilization, in which case no additional contraception is needed. Pregnancy must also be excluded if treatment is interrupted for more than 14 days in females of reproductive potential.

1 INDICATIONS AND USAGE

KORLYM (mifepristone) is a cortisol receptor blocker indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.

LIMITATIONS OF USE:

- KORLYM should not be used in the treatment of patients with type 2 diabetes unless it is secondary to Cushing's syndrome.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosage

The recommended starting dose is 300 mg orally once daily. KORLYM must be given as a single daily dose. KORLYM should always be taken with a meal. Patients should swallow the tablet whole. Do not split, crush, or chew tablets.

Dosing and titration

The daily dose of KORLYM may be increased in 300 mg increments. The dose of KORLYM may be increased to a maximum of 1200 mg once daily but should not exceed 20 mg/kg per day. Increases in dose should not occur more frequently than once every 2-4 weeks. Decisions about dose increases should be based on a clinical assessment of tolerability and degree of improvement in Cushing's syndrome manifestations. Changes in glucose control, anti-diabetic medication requirements, insulin levels, and psychiatric symptoms may provide an early assessment of response (within 6 weeks) and may help guide early dose titration. Improvements in cushingoid appearance, acne, hirsutism, striae, and body weight occur over a longer period of time and, along with measures of glucose control, may be used to determine dose changes beyond the first 2 months of therapy. Careful and gradual titration of KORLYM accompanied by monitoring for recognized adverse reactions (*See Warnings and Precautions 5.1 and 5.2*) may reduce the risk of severe adverse reactions. Dose reduction or even dose discontinuation may be needed in some clinical situations. If KORLYM treatment is interrupted, it should be reinitiated at the lowest dose (300 mg). If treatment was interrupted because of adverse reactions, the titration should aim for a dose lower than the one that resulted in treatment interruption.

2.2 Dosing in Renal Impairment

No change in initial dose of KORLYM is required in renal impairment. The maximum dose should be limited to 600 mg. *[See Renal Impairment (8.6) and Clinical Pharmacology (12.3)]*

2.3 Dosing in Hepatic Impairment

No change in the initial dose of KORLYM is required in mild to moderate hepatic impairment. The maximum dose should be limited to 600 mg. KORLYM should not be used in severe hepatic impairment. *[See Hepatic Impairment (8.7) and Clinical Pharmacology (12.3)]*

2.4 Concomitant Administration with CYP3A Inhibitors

Ketoconazole and other strong inhibitors of CYP3A, such as itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir and fosamprenavir, clarithromycin, conivaptan, lopinavir/ritonavir, posaconazole, saquinavir, telithromycin, or voriconazole may increase exposure to mifepristone. KORLYM should be used in combination with strong CYP3A inhibitors only when necessary. [See Warnings and Precautions (5.6), Drug Interactions (7.2)]

Administration of KORLYM to patients already being treated with strong CYP3A inhibitors:

- Start at a dose of 300 mg. If clinically indicated, titrate to a maximum of 600 mg.

Administration of strong CYP3A inhibitors to patients already being treated with KORLYM:

- Adjust the dose of KORLYM according to Table 1.

Table 1. Dose adjustment of KORLYM when strong CYP3A inhibitor is added

Current dose of KORLYM	Adjustment to dose of KORLYM if adding a strong CYP3A inhibitor
300 mg	No change
600 mg	Reduce dose to 300 mg. If clinically indicated, titrate to a maximum of 600 mg
900 mg	Reduce dose to 600 mg
1200 mg	Reduce dose to 600 mg

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3 DOSAGE FORMS AND STRENGTHS

Tablets: 300 mg

Oval shaped, light yellow to yellow tablets debossed with "Corcept" on one side and "300" on the other side. The tablets are not scored.

4 CONTRAINDICATIONS

4.1 Pregnancy

KORLYM is contraindicated in women who are pregnant. Pregnancy must be excluded before the initiation of treatment with KORLYM or if treatment is interrupted for more than 14 days in females of

reproductive potential. Non-hormonal contraceptives should be used during and one month after stopping treatment in all women of reproductive potential. *[See Use in Specific Populations 8.8]*

4.2 Drugs Metabolized by CYP3A

KORLYM is contraindicated in patients taking simvastatin, lovastatin, and CYP3A substrates with narrow therapeutic ranges, such as cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, due to an increased risk of adverse events. *[See Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*

4.3 Corticosteroid Therapy Required for Lifesaving Purposes

KORLYM is contraindicated in patients who require concomitant treatment with systemic corticosteroids for serious medical conditions or illnesses (e.g., immunosuppression after organ transplantation) because KORLYM antagonizes the effect of glucocorticoids.

4.4 Women with Risk of Vaginal Bleeding or Endometrial Changes

KORLYM is contraindicated in the following:

- Women with a history of unexplained vaginal bleeding
- Women with endometrial hyperplasia with atypia or endometrial carcinoma

4.5 Known Hypersensitivity to Mifepristone

KORLYM is contraindicated in patients with prior hypersensitivity reactions to mifepristone or to any of the product components.

5 WARNINGS AND PRECAUTIONS

5.1 Adrenal Insufficiency

Patients receiving mifepristone may experience adrenal insufficiency. Because serum cortisol levels remain elevated and may even increase during treatment with KORLYM, serum cortisol levels do not provide an accurate assessment of hypoadrenalism in patients receiving KORLYM. Patients should be closely monitored for signs and symptoms of adrenal insufficiency, including weakness, nausea, increased fatigue, hypotension, and hypoglycemia. If adrenal insufficiency is suspected, discontinue treatment with KORLYM immediately and administer glucocorticoids without delay. High doses of supplemental glucocorticoids may be needed to overcome the glucocorticoid receptor blockade produced by mifepristone. Factors considered in deciding on the duration of glucocorticoid treatment should include the long half-life of mifepristone (85 hours).

Treatment with KORLYM at a lower dose can be resumed after resolution of adrenal insufficiency. Patients should also be evaluated for precipitating causes of hypoadrenalism (infection, trauma, etc.).

5.2 Hypokalemia

In a study of patients with Cushing's syndrome, hypokalemia was observed in 44% of subjects during treatment with KORLYM. Hypokalemia should be corrected prior to initiating KORLYM. During KORLYM administration, serum potassium should be measured 1 to 2 weeks after starting or increasing the dose of KORLYM and periodically thereafter. Hypokalemia can occur at any time during KORLYM

treatment. Mifepristone-induced hypokalemia should be treated with intravenous or oral potassium supplementation based on event severity. If hypokalemia persists in spite of potassium supplementation, consider adding mineralocorticoid antagonists.

5.3 Vaginal Bleeding and Endometrial Changes

Being an antagonist of the progesterone receptor, mifepristone promotes unopposed endometrial proliferation that may result in endometrium thickening, cystic dilatation of endometrial glands, and vaginal bleeding. KORLYM should be used with caution in women who have hemorrhagic disorders or are receiving concurrent anticoagulant therapy. Women who experience vaginal bleeding during KORLYM treatment should be referred to a gynecologist for further evaluation.

5.4 QT Interval Prolongation

Mifepristone and its metabolites block IKr. KORLYM prolongs the QTc interval in a dose-related manner. There is little or no experience with high exposure, concomitant dosing with other QT-prolonging drugs, or potassium channel variants resulting in a long QT interval. *[See Warnings & Precautions (5.6)]* To minimize risk, the lowest effective dose should always be used.

5.5 Exacerbation/Deterioration of Conditions Treated with Corticosteroids

Use of KORLYM in patients who receive corticosteroids for other conditions (e.g., autoimmune disorders) may lead to exacerbation or deterioration of such conditions, as KORLYM antagonizes the desired effects of glucocorticoid in these clinical settings. For medical conditions in which chronic corticosteroid therapy is lifesaving (e.g., immunosuppression in organ transplantation), KORLYM is contraindicated. *[See Contraindications (4.3)]*

5.6 Use of Strong CYP3A Inhibitors

KORLYM should be used with caution in patients taking ketoconazole and other strong inhibitors of CYP3A, such as itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, clarithromycin, conivaptan, lopinavir/ritonavir, posaconazole, saquinavir, telithromycin, or voriconazole, as these could increase the concentration of mifepristone in the blood. The benefit of concomitant use of these agents should be carefully weighed against the potential risks. KORLYM should be used in combination with strong CYP3A inhibitors only when necessary, and in such cases the dose should be limited to 600 mg per day. *[See Warnings & Precautions (5.4), Drug Interactions (7.2), and Clinical Pharmacology (12.3)]*

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5.7 *Pneumocystis jiroveci* Infection

Patients with endogenous Cushing's syndrome are at risk for opportunistic infections such as *Pneumocystis jiroveci* pneumonia during KORLYM treatment. Patients may present with respiratory distress shortly after initiation of KORLYM. Appropriate diagnostic tests should be undertaken and treatment for *Pneumocystis jiroveci* should be considered.

5.8 Potential Effects of Hypercortisolemia

KORLYM does not reduce serum cortisol levels. Elevated cortisol levels may activate mineralocorticoid receptors which are also expressed in cardiac tissues. Caution should be used in patients with underlying heart conditions including heart failure and coronary vascular disease.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

Safety data on the use of KORLYM are available from 50 patients with Cushing's syndrome enrolled in an uncontrolled, open-label, multi-center trial (Study 400). Forty-three patients had Cushing's disease and all except one had previously undergone pituitary surgery. Four patients had ectopic ACTH secretion, and three had adrenal carcinoma. Patients were treated for up to 24 weeks. A dose of 300 mg per day was administered for the initial 14 days; thereafter, the dose could be escalated in increments of 300 mg per day based on assessments of tolerability and clinical response. Doses were escalated up to 900 mg per day for patients <60 kg, or 1200 mg per day for patients >60 kg.

The most frequently reported adverse reactions (reported in ≥20% of patients, regardless of relationship to KORLYM) were nausea, fatigue, headache, decreased blood potassium, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite, and endometrial hypertrophy. Drug-related adverse events resulted in dose interruption or reduction in study drug in 40% of patients.

The adverse reactions that occurred in ≥10% of the Cushing's syndrome patients receiving KORLYM, regardless of relationship to KORLYM, are shown in Table 2.

Table 2. Treatment Emergent Adverse Events Occurring in ≥10% of Cushing's Syndrome Patients Receiving KORLYM

Body System/Adverse Reaction	Percent (%) of Patients Reporting Event (n = 50)
Gastrointestinal disorders	
Nausea	48
Vomiting	26
Dry mouth	18
Diarrhea	12
Constipation	10
General disorders and administration/site conditions	
Fatigue	48
Edema peripheral	26
Pain	14
Nervous system disorders	
Headache	44
Dizziness	22
Somnolence	10
Musculoskeletal and connective tissue disorders	
Arthralgia	30
Back pain	16
Myalgia	14
Pain in extremity	12
Investigations	
Blood potassium decreased	34
Thyroid function test abnormal	18
Infections and infestations	
Sinusitis	14
Nasopharyngitis	12
Metabolism and nutrition disorders	
Decreased appetite	20
Anorexia	10
Vascular disorders	
Hypertension	24
Reproductive system and breast disorders	
Endometrial hypertrophy	38*
Respiratory, thoracic, and mediastinal disorders	
Dyspnea	16
Psychiatric disorders	
Anxiety	10

*The denominator was 26 females who had baseline and end-of-trial transvaginal ultrasound

Laboratory Tests

Reductions in high density lipoprotein-cholesterol (HDL-C) levels have been observed following treatment with KORLYM. In study subjects that experienced declines in HDL-C, levels returned to baseline following discontinuation of drug. The clinical significance of the treatment-related reduction in HDL-C levels in patients with Cushing's syndrome is not known.

In a study of patients with Cushing's syndrome, hypokalemia was observed in 44% of subjects during treatment with KORLYM. In these cases, hypokalemia responded to treatment with potassium supplementation and/or mineralocorticoid antagonist therapy (e.g., spironolactone or eplerenone). Hypokalemia should be corrected prior to initiating KORLYM. *[See Warnings and Precautions (5.2)]*

Elevations of thyroid-stimulating hormone (TSH) were seen in subjects treated with KORLYM. Of the 42 subjects with detectable TSH at baseline, eight (19%) had increases in TSH above the normal range, while remaining asymptomatic. The TSH levels returned to normal in most patients without intervention when KORLYM was discontinued at the end of the study.

Vaginal Bleeding and Endometrial Changes

In Study 400, the thickness of the endometrium increased from a mean of 6.14 mm at baseline (n=23) to 15.7 mm at end-of-trial (n=18) in premenopausal women; in postmenopausal women the increase was from 2.75 mm (n=6) to 7.35 mm (n=8). Endometrial thickness above the upper limit of normal was reported in 10/26 females who had baseline and end-of-trial transvaginal ultrasound (38%). The endometrial thickness returned to the normal range in 3 out of 10 patients 6 weeks after treatment cessation at the end of the study. Vaginal bleeding occurred in 5 out of 35 females (14%). Two of five subjects with vaginal bleeding had normal endometrial thickness. Endometrial biopsies were performed in six patients; five of these patients had endometrial thickening. No endometrial carcinoma was detected in the sampled cases.

Additional Data from Clinical Trials

The following are adverse events that were reported in Study 400 at frequencies of ≥ 5% to 10%, and may be related to KORLYM's mechanism of action:

Gastrointestinal disorders: gastroesophageal reflux, abdominal pain

General disorders and administration site conditions: asthenia, malaise, edema, pitting edema, thirst

Investigations: blood triglycerides increased

Metabolism and nutrition disorders: hypoglycemia

Musculoskeletal and connective tissue disorders: muscular weakness, flank pain, musculoskeletal chest pain

Psychiatric disorders: insomnia

Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia *[See Warnings and Precautions (5.3)]*

Adrenal Insufficiency

Adrenal insufficiency was reported in two subjects (4%) in Study 400. The most typical symptoms of adrenal insufficiency were nausea and decreased appetite. No hypotension or hypoglycemia was reported

during the events. Adrenal insufficiency resolved in both cases with KORLYM interruption and /or dexamethasone administration.

Rash

Generalized, maculo-papular rash was reported in 2 subjects (4%) in Study 400. Two additional subjects developed pruritus (4%). None resulted in discontinuation of KORLYM, and all the events resolved by the end of the study.

6.2 Postmarketing Experience

The following adverse reaction has been identified during post approval use of KORLYM. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Angioedema

7 DRUG INTERACTIONS

Based on the long terminal half-life of mifepristone after reaching steady state, at least 2 weeks should elapse after cessation of KORLYM before initiating or increasing the dose of any interacting concomitant medication.

7.1 Drugs Metabolized by CYP3A

Because KORLYM is an inhibitor of CYP3A, concurrent use of KORLYM with a drug whose metabolism is largely or solely mediated by CYP3A is likely to result in increased plasma concentrations of the drug. Discontinuation or dose reduction of such medications may be necessary with KORLYM co-administration.

KORLYM increased the exposure to simvastatin and simvastatin acid significantly in healthy subjects. Concomitant use of simvastatin or lovastatin is contraindicated because of the increased risk of myopathy and rhabdomyolysis. *[See Contraindications (4.2), Clinical Pharmacology 12.3]*

The exposure of other substrates of CYP3A with narrow therapeutic ranges, such as cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, may be increased by concomitant administration with KORLYM. Therefore, the concomitant use of such CYP3A substrates with KORLYM is contraindicated. *[See Contraindications (4.2)]*

Other drugs with similar high first pass metabolism in which CYP3A is the primary route of metabolism should be used with extreme caution if co-administered with KORLYM. The lowest possible dose and/or a decreased frequency of dosing must be used with therapeutic drug monitoring when possible. Use of alternative drugs without these metabolic characteristics is advised when possible with concomitant KORLYM.

If drugs that undergo low first pass metabolism by CYP3A or drugs in which CYP3A is not the major metabolic route are co-administered with KORLYM, use the lowest dose of concomitant medication necessary, with appropriate monitoring and follow-up. *[See Clinical Pharmacology (12.3)]*

7.2 CYP3A Inhibitors

Medications that inhibit CYP3A could increase plasma mifepristone concentrations and dose reduction of KORLYM may be required.

Ketoconazole and other strong inhibitors of CYP3A, such as itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir and fosamprenavir, clarithromycin, conivaptan, lopinavir/ritonavir, posaconazole, saquinavir, telithromycin, or voriconazole may increase exposure to mifepristone. Caution should be used when strong CYP3A inhibitors are prescribed in combination with KORLYM. The benefit of concomitant use of these agents should be carefully weighed against the potential risks. The dose of KORLYM should be limited to 600 mg, and strong inhibitors of CYP3A should be used only when necessary. *[See Dosage and Administration (2.4), Warnings & Precautions (5.6), and Clinical Pharmacology (12.3)]*

7.3 CYP3A Inducers

No medications that induce CYP3A have been studied when co-administered with KORLYM. Avoid co-administration of KORLYM and CYP3A inducers such as rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine, and St. John's wort.

7.4 Drugs Metabolized by CYP2C8/2C9

Because KORLYM is an inhibitor of CYP2C8/2C9, concurrent use of KORLYM with a drug whose metabolism is largely or solely mediated by CYP2C8/2C9 is likely to result in increased plasma concentrations of the drug.

KORLYM significantly increased exposure of fluvastatin, a typical CYP2C8/2C9 substrate, in healthy subjects. When given concomitantly with KORLYM, drugs that are substrates of CYP2C8/2C9 (including non-steroidal anti-inflammatory drugs, warfarin, and repaglinide) should be used at the smallest recommended doses, and patients should be closely monitored for adverse effects. *[See Clinical Pharmacology (12.3)]*

7.5 Drugs Metabolized by CYP2B6

Mifepristone is an inhibitor of CYP2B6 and may cause significant increases in exposure of drugs that are metabolized by CYP2B6 such as bupropion and efavirenz. Since no study has been conducted to evaluate the effect of mifepristone on substrates of CYP2B6, the concomitant use of bupropion and efavirenz should be undertaken with caution. *[See Clinical Pharmacology (12.3)]*

7.6 Use of Hormonal Contraceptives

Mifepristone is a progesterone-receptor antagonist and will interfere with the effectiveness of hormonal contraceptives. Therefore, non-hormonal contraceptive methods should be used.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Category X

KORLYM is contraindicated in pregnancy. KORLYM can cause fetal harm when administered to a pregnant woman because the use of KORLYM results in pregnancy loss. The inhibition of both endogenous and exogenous progesterone by mifepristone at the progesterone receptor results in pregnancy loss. If KORLYM is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. *[See Contraindications (4.1)]*

Human Data

In a report of thirteen live births after single dose mifepristone exposure, no fetal abnormalities were noted.

Animal Data

Teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than human exposure at the maximum clinical dose, based on body surface area) were carried out. Because of the anti-progestational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at less than human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from antagonism of the progesterone receptor.

8.3 Nursing Mothers

Mifepristone is present in human milk of women taking the drug. Because of the potential for serious adverse reactions in nursing infants from KORLYM, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of KORLYM in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies with KORLYM did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger people.

8.6 Renal Impairment

The maximum dose should not exceed 600 mg per day in renally impaired patients. *[See Clinical Pharmacology (12.3)]*

8.7 Hepatic Impairment

In patients with mild to moderate hepatic impairment, the maximum dose should not exceed 600 mg per day. The pharmacokinetics of mifepristone in patients with severe hepatic impairment has not been studied, and KORLYM should not be used in these patients. *[See Clinical Pharmacology (12.3)]*

8.8 Females of Reproductive Potential

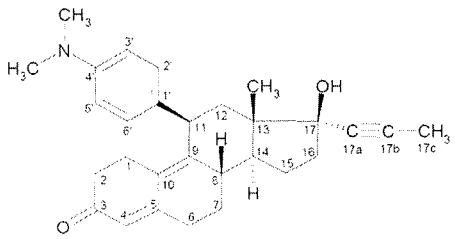
Due to its anti-progestational activity, KORLYM causes pregnancy loss. Exclude pregnancy before the initiation of treatment with KORLYM or if treatment is interrupted for more than 14 days in females of reproductive potential. Recommend contraception for the duration of treatment and for one month after stopping treatment using a non-hormonal medically acceptable method of contraception. If the patient has had surgical sterilization, no additional contraception is needed.

10 OVERDOSAGE

There is no experience with overdosage of KORLYM.

11 DESCRIPTION

KORLYM (mifepristone) is a cortisol receptor blocker for oral administration. The chemical name of mifepristone is 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(1-propynyl)-estra-4, 9-dien-3-one. The chemical formula is $C_{29}H_{35}NO_2$; the molecular weight is 429.60, and the structural formula is:



Mifepristone demonstrates a pH-related solubility profile. The greatest solubility is achieved in acidic media (~ 25 mg/mL at pH 1.5) and solubility declines rapidly as the pH is increased. At pH values above 2.5 the solubility of mifepristone is less than 1 mg/mL.

Each KORLYM tablet for oral use contains 300 mg of mifepristone. The inactive ingredients of KORLYM tablets are silicified microcrystalline cellulose, sodium starch glycolate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate, hypromellose, titanium dioxide, triacetin, D&C yellow 10 aluminum lake, polysorbate 80, and FD&C yellow 6 aluminum lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mifepristone is a selective antagonist of the progesterone receptor at low doses and blocks the glucocorticoid receptor (GR-II) at higher doses. Mifepristone has high affinity for the GR-II receptor but little affinity for the GR-I (MR, mineralocorticoid) receptor. In addition, mifepristone appears to have little or no affinity for estrogen, muscarinic, histaminic, or monoamine receptors.

12.2 Pharmacodynamics

Because mifepristone acts at the receptor level to block the effects of cortisol, its antagonistic actions affect the hypothalamic-pituitary-adrenal (HPA) axis in such a way as to further increase circulating cortisol levels while, at the same time, blocking their effects.

Mifepristone and the three active metabolites have greater affinity for the glucocorticoid receptor [100% (mifepristone), 61% (metabolite 1), 48% (metabolite 2), and 45% (metabolite 3)] than either dexamethasone (23%) or cortisol (9%).

12.3 Pharmacokinetics

Absorption

Following oral administration, time to peak plasma concentrations of mifepristone occurred between 1 and 2 hours following single dose, and between 1 and 4 hours following multiple doses of 600 mg of KORLYM in healthy volunteers. Mean plasma concentrations of three active metabolites of mifepristone peak between 2 and 8 hours after multiple doses of 600 mg/day, and the combined concentrations of the metabolites exceed that of the parent mifepristone. Exposure to mifepristone is substantially less than dose proportional. Time to steady state is within 2 weeks, and the mean (SD) half-life of the parent mifepristone was 85 (61) hours following multiple doses of 600 mg/day of KORLYM.

Studies evaluating the effects of food on the pharmacokinetics of KORLYM demonstrate a significant increase in plasma levels of mifepristone when dosed with food. To achieve consistent plasma drug concentrations, patients should be instructed to always take their medication with meals.

Distribution

Mifepristone is highly bound to alpha-1-acid glycoprotein (AAG) and approaches saturation at doses of 100 mg (2.5 μM) or more. Mifepristone and its metabolites also bind to albumin and are distributed to other tissues, including the central nervous system (CNS). As determined in vitro by equilibrium dialysis, binding of mifepristone and its three active metabolites to human plasma proteins was concentration-dependent. Binding was approximately 99.2% for mifepristone, and ranged from 96.1 to 98.9% for the three active metabolites at clinically relevant concentrations.

Metabolism

Cytochrome P450 3A4 (CYP3A4) has been shown to be involved in mifepristone metabolism in human liver microsomes. Two of the known active metabolites are the product of demethylation (one monodemethylated and one di-demethylated), while a third active metabolite results from hydroxylation (monohydroxylated).

Elimination and Excretion

Excretion is primarily (approximately 90%) via the fecal route.

Specific Populations

Renal Impairment

The pharmacokinetics of mifepristone in subjects with severe renal impairment (creatinine clearance [CrCL] < 30 mL/min, but not on dialysis) was evaluated following multiple doses of 1200 mg KORLYM for 7 days. Mean exposure to mifepristone increased 31%, with similar or smaller increases in metabolite exposure as compared to subjects with normal renal function (CrCL ≥ 90 mL/min). There was large variability in the exposure of mifepristone and its metabolites in subjects with severe renal impairment as compared to subjects with normal renal function (geometric least square mean ratio [CI] for AUC of mifepristone: 1.21 [0.71-2.06]; metabolite 1: 1.43 [0.84-2.44]; metabolite 2: 1.18 [0.64-2.17] and metabolite 3: 1.19 [0.71-1.99]). No change in the initial dose of KORLYM is needed for renal impairment; the maximum dose should not exceed 600 mg per day.

Hepatic Impairment

The pharmacokinetics of mifepristone in subjects with moderate hepatic impairment (Child-Pugh Class B) was evaluated in a single- and multiple-dose study (600 mg for 7 days). The pharmacokinetics in subjects with moderate hepatic impairment was similar to those with normal hepatic function. There was large variability in the exposure of mifepristone and its metabolites in subjects with moderate hepatic impairment as compared to subjects with normal hepatic function (geometric least square mean ratio [CI] for AUC of mifepristone: 1.02 [0.59-1.76]; metabolite 1: 0.95 [0.52-1.71]; metabolite 2: 1.37 [0.71-2.62] and metabolite 3: 0.62 [0.33-1.16]). Due to limited information on safety in patients with mild-to-moderate hepatic impairment, the maximum dose should not exceed 600 mg per day. The pharmacokinetics of mifepristone in patients with severe hepatic disease has not been studied. KORLYM is not recommended in patients with severe hepatic disease.

Drug-Drug Interactions

In Vitro Assessment of Drug Interactions

In vitro studies indicate a potential for CYP-mediated drug interactions by mifepristone and/or its metabolites with substrates of CYP2A6, CYP2C8/2C9, CYP2C19, CYP3A4, CYP1A2, CYP2B6, CYP2D6, and CYP2E1. In vitro studies also indicated an interaction potential for drug transport mediated by P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). In vitro studies indicate mifepristone metabolism is mediated by CYP3A, and that mifepristone also inhibits and induces CYP3A.

In Vivo Assessment of Drug Interactions (see Table 3)

Table 3. Summary Table of KORLYM Drug-Drug Interaction Effects

Dosing of Mifepristone	Coadministered Drug	Dosing of Coadministered Drug	Geometric Mean Ratio (analyte ratio with/without drug coadministration)		
			Analyte	AUC	Cmax
Effect of KORLYM on Coadministered Drug					
Contraindicated with mifepristone *[See Contraindications (4)]*					
1200 mg once daily for 10 days	simvastatin[1]	80 mg single dose	simvastatin acid	15.70	18.20
			simvastatin	10.40	7.02
Use lowest dose of coadministered drug, based on clinical experience and/or use of therapeutic drug monitoring					
1200 mg once daily for 10 days	alprazolam[2]	1 mg single dose	alprazolam	1.80	0.81
			4-hydroxy-alprazolam	0.76	0.39
1200 mg once daily for 7 days	fluvastatin[3]	40 mg single dose	fluvastatin	3.57	1.76
1200 mg once daily for 10 days	digoxin[4]	0.125 mg once daily	digoxin	1.40	1.64
Effect of Coadministered Drug on KORLYM					
Dose adjustment required					
600 mg once daily for 17 days	ketoconazole	200 mg bid on days 13-17	mifepristone	1.38	1.28
			Metabolite 1†	1.02	1.06

			Metabolite 2†	1.67	1.69
			Metabolite 3†	0.95	0.96
Effect of Coadministered Drug on KORLYM					
No dosing adjustment required					
300 mg once daily for 14 days	cimetidine[5]	800 mg once daily	mifepristone	0.85*	0.75

*No effect = 90% CI within range 0.80 – 1.25

†See Section 12.2 for the relative potencies of the three metabolites

[1] Simvastatin 40 mg dose used as reference for the comparison. Result could be representative of other oral drugs with CYP3A metabolism and high first pass effect: cyclosporine, midazolam, triazolam, pimozide, sildenafil, sirolimus, and tacrolimus

[2] Result could be representative of other oral drugs with CYP3A metabolism and low first pass effect. Clinical significance of any interaction will depend on the therapeutic margin of the drug.

[3] Result could be representative of other oral drugs with CYP2C8/C9 metabolism

[4] Plasma digoxin concentration should be measured after 1 to 2 weeks of concomitant use and following usual clinical practice at appropriate intervals thereafter.

[5]Result could be representative of other mild inhibitors of CYP3A

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Mifepristone was evaluated for carcinogenicity potential in rats and mice. Rats were dosed for up to two years at doses of 5, 25, and 125 mg/kg of mifepristone. The high dose was the maximum tolerated dose, but exposure at all doses was below exposure at the maximum clinical dose based on AUC comparison. Female rats had a statistically significant increase in follicular cell adenomas/carcinomas and liver adenomas. It is plausible that these tumors are due to drug-induced enzyme metabolism, a mechanism not considered clinically relevant, but studies confirming this mechanism were not conducted with mifepristone. Mice were also tested for up to 2 years at mifepristone doses up to the maximum tolerated dose of 125 mg/kg, which provided exposure below the maximum clinical dose based on AUC. No drug-related tumors were seen in mice.

Mifepristone was not genotoxic in a battery of bacterial, yeast, and mammalian in vitro assays, and an in vivo micronucleus study in mice.

The pharmacological activity of mifepristone disrupts the estrus cycle of adult rats at a dose of 0.3 mg/kg (less than human exposure at the maximum clinical dose, based on body surface area). However, following withdrawal of treatment and subsequent resumption of the estrus cycle, there was no effect on reproductive function when mated.

A single subcutaneous dose of mifepristone (up to 100 mg/kg) to rats on the first day after birth did not adversely affect future reproductive function in males or females, although the onset of puberty was slightly premature in dosed females. Repeated doses of mifepristone (1 mg every other day) to neonatal rats resulted in potentially adverse fertility effects, including oviduct and ovary malformations in females,

delayed male puberty, deficient male sexual behavior, reduced testicular size, and lowered ejaculation frequency.

14 CLINICAL STUDIES

14.1 Cushing's Syndrome

An uncontrolled, open-label, 24-week, multicenter clinical study was conducted to evaluate the safety and efficacy of KORLYM in the treatment of endogenous Cushing's syndrome. The study enrolled 50 subjects with clinical and biochemical evidence of hypercortisolemia despite prior surgical treatment and radiotherapy. The reasons for medical treatment were failed surgery, recurrence of disease, and poor medical candidate for surgery. Forty-three patients (86%) had Cushing's disease, four patients (8%) had ectopic ACTH secretion, and three (6%) had adrenal carcinoma. Baseline characteristics included: mean age of 45 years (range 26 to 71), mean BMI of 36 kg/m^2 (range 24 to 66), mean weight 100 kg (range 61 to 199), and mean waist circumference was 119 cm (range 89 to 178); 70% were female; 84% were white and 16% were black or African American. Baseline mean urinary free cortisol level was 365 µg per 24 hr.

Patients belonged to one of two cohorts: a "diabetes" cohort (29 patients, 26 with type 2 diabetes and 3 with glucose intolerance), and a "hypertension" cohort (21 patients). Efficacy was evaluated separately in the two cohorts. KORLYM treatment was started in all patients at a dose of 300 mg once a day. The study protocol allowed an increase in dose to 600 mg after 2 weeks, and then by additional 300 mg increments every 4 weeks to a maximum of 900 mg per day for patients ≤60 kg, or 1200 mg per day for patients >60 kg, based on clinical tolerance and clinical response.

Results in the diabetes cohort

Patients in the diabetes cohort underwent standard oral glucose tolerance tests at baseline and periodically during the clinical study. Anti-diabetic medications were allowed but had to be kept stable during the trial and patients had to be on stable anti-diabetic regimens prior to enrollment. The primary efficacy analysis for the diabetes cohort was an analysis of responders. A responder was defined as a patient who had a ≥ 25% reduction from baseline in glucose AUC. The primary efficacy analysis was conducted in the modified intent-to-treat population (n=25) defined as all patients who received a minimum of 30 days on KORLYM. Fifteen of 25 patients (60%) were treatment responders (95% CI: 39%,78%).

Mean HbA1c was 7.4% in the 24 patients with HbA1c values at baseline and Week 24. For these 24 patients mean reduction in HbA1c was 1.1% (95% CI -1.6, -0.7) from baseline to the end of the trial. Fourteen of 24 patients had above normal HbA1c levels at baseline, ranging between 6.7% and 10.4%; all of these patients had reductions in HbA1c by the end of the study (range -0.4 to -4.4%) and eight of 14 patients (57%) normalized HbA1c levels at trial end. Antidiabetic medications were reduced in 7 of the 15 DM subjects taking antidiabetic medication and remained constant in the others.

Results in the hypertension cohort

There were no changes in mean systolic and diastolic blood pressures at the end of the trial relative to baseline in the modified intent-to-treat population (n=21).

Signs and symptoms of Cushing's syndrome in both cohorts

Individual patients showed varying degrees of improvement in Cushing's syndrome manifestations such as cushingoid appearance, acne, hirsutism, striae, psychiatric symptoms, and excess total body weight. Because of the variability in clinical presentation and variability of response in this open label trial, it is uncertain whether these changes could be ascribed to the effects of KORLYM.

16 HOW SUPPLIED/STORAGE AND HANDLING

KORLYM is supplied as a light yellow to yellow, film-coated, oval-shaped tablet debossed with "Corcept" on one side and "300" on the other. Each tablet contains 300 mg of mifepristone. KORLYM tablets are available in bottles of 28 tablets (NDC 76346-073-01) and bottles of 280 tablets (NDC 76346-073-02).

Store at controlled room temperature, 25 °C (77 °F); excursions permitted to 15 to 30 °C (59 – 86 °F). *[See USP Controlled Room Temperature]*

17 PATIENT COUNSELING INFORMATION

As a part of patient counseling, doctors must review the KORLYM Medication Guide with every patient.

17.1 Importance of Preventing Pregnancy

- Advise patients that KORLYM will cause termination of pregnancy. KORLYM is contraindicated in pregnant patients.
- Counsel females of reproductive potential regarding pregnancy prevention and planning with a non-hormonal contraceptive prior to use of KORLYM and up to one month after the end of treatment.
- Instruct patients to contact their physician immediately if they suspect or confirm they are pregnant.

Medication Guide
KORLYM® (KOR-Lim)
(mifepristone)
tablets

What is the most important information I should know about KORLYM?

KORLYM can cause serious side effects, including:

- **Loss of a pregnancy.** Women who can become pregnant must:
  - have a negative pregnancy test before starting KORLYM
  - have a negative pregnancy test before restarting KORLYM if you stop taking it for more than 14 days
  - use a non-hormonal form of birth control while taking KORLYM and for 1 month after stopping KORLYM. Talk to your doctor about how to prevent pregnancy. Tell your doctor right away if you think you may be pregnant.

What is KORLYM?

KORLYM is a prescription medicine used to treat high blood sugar (hyperglycemia) caused by high cortisol levels in the blood (hypercortisolism) in adults with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or cannot have surgery.

KORLYM is not for people who have type 2 diabetes mellitus not caused by Cushing's syndrome.

It is not known if KORLYM is safe and effective in children.

Do not take KORLYM if you:

- **are pregnant.** See "What is the most important information I should know about KORLYM?"
- **are taking:**
  - simvastatin (Zocor®, Vytorin®, Juvisync®, Simcor®)
  - lovastatin (Mevacor®, Altoprev®, Advicor®)
  - cyclosporine (Gengraf®, Neoral®, Restasis®, Sandimmune®)
  - dihydroergotamine (Migranal®)
  - ergotamine (Ergomar®, Migergot®)
  - fentanyl (Abstral®, Actiq®, Duragesic®, Fentora®, Lazanda®, Onsolis®, Sublimaze Preservative Free®, Subsys®)
  - pimozide (Orap®)
  - quinidine (Neudexta®)
  - sirolimus (Rapamune®, Torisel®)
  - tacrolimus (Prograf®, Protopic®)
- must take corticosteroid medicines for other serious medical problems
- are a woman who still has her uterus (womb) **and** have:
  - unexplained bleeding from your vagina
  - changes in the cells lining your uterus (endometrial hyperplasia) or cancer of the lining of your uterus (endometrial cancer)
- are allergic to mifepristone or any of the ingredients in KORLYM. See the end of this Medication Guide for a complete list of ingredients in KORLYM.

Talk to your doctor before taking KORLYM if you have any of these conditions.

What should I tell my doctor before taking KORLYM?

Before taking KORLYM, tell your doctor if you:

- have low potassium in your blood (hypokalemia)
- have or have had a bleeding problem or are taking medicines to thin your blood
- have or have had heart problems
- have had an organ transplant

  have been taking medicines called corticosteroids (cortisone, dexamethasone, methylprednisolone, prednisolone, prednisone)
- are breastfeeding or plan to breastfeed. KORLYM passes into your breast milk and may harm your baby. You and your doctor should decide if you will take KORLYM or breastfeed. You should not do both.

Tell your doctor about all of the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements.

Using **KORLYM** with certain other medicines can affect each other. Using KORLYM with other medicines can cause serious side effects.

Especially tell your doctor if you take:

- medicines to treat:
  - fungal infections (such as ketoconazole)
  - depression
  - HIV infection
  - Hepatitis C infection
  - certain bacterial infections
  - high blood pressure
- steroid medicines such as prednisone
- thyroid hormones

Ask your doctor or pharmacist for a list of these medicines if you are not sure. Know the medicines you take. Keep a list of them to show to your doctor and pharmacist.

How should I take KORLYM?

- Take KORLYM exactly as your doctor tells you.
- Your doctor may change your dose if needed.
- KORLYM is usually taken 1 time each day.
- Take KORLYM with food.
- Swallow KORLYM whole. **Do not** split, crush or chew KORLYM tablets. If you cannot swallow KORLYM tablets whole, tell your doctor.

What should I avoid while taking KORLYM?

You should not drink grapefruit juice while you take KORLYM. Grapefruit juice may increase the amount of KORLYM in your blood and increase your chance of having side effects.

What are the possible side effects of KORLYM?

KORLYM can cause serious side effects including:

- **See "What is the most important information I should know about KORLYM?"**
- **reduced effects of adrenal hormones (adrenal insufficiency).** KORLYM stops an adrenal hormone in your body called cortisol from working. Tell your doctor right away if you have any symptoms of adrenal insufficiency. Symptoms may include:
  - unusual tiredness or weakness
  - nausea
  - fatigue
  - low blood pressure (hypotension)
  - low blood sugar (hypoglycemia)
- **low blood potassium (hypokalemia).** Your doctor should check the level of potassium in your blood before you start taking KORLYM and while you take it. Tell your doctor if you have any signs of low potassium. Signs may include:
  - muscle weakness, aches, or cramps
  - abnormal or irregular heartbeats (palpitations)
- **bleeding from the vagina.** KORLYM may cause the lining of your uterus to become thick and may cause your uterus to bleed. Tell your doctor right away about any bleeding from your vagina that is not normal for you.
- **problems with the electrical system of your heart (QT interval prolongation).**
- **worsening of symptoms of other medical problems that are treated with corticosteroids when you take corticosteroids and KORLYM at the same time.**

The most common side effects of **KORLYM** include:

- nausea
- headache
- pain in your arms and legs (arthralgia)
- fatigue
- low potassium in your blood
- vomiting

- swelling of your arms and legs (peripheral edema)
- high blood pressure
- dizziness
- decreased appetite
- thickening of the lining of the uterus (endometrial hypertrophy)

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of KORLYM.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store KORLYM?

Store KORLYM at room temperature, between 68°F to 77°F (20°C to 25°C).

Keep KORLYM and all medicines out of the reach of children.

General information about the safe and effective use of KORLYM

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

Do not use KORLYM for a condition for which it was not prescribed. Do not give KORLYM to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about KORLYM that is written for healthcare professionals.

What are the ingredients in KORLYM?

Active ingredient: mifepristone

Inactive ingredients: silicified microcrystalline cellulose, sodium starch glycolate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate, hypromellose, titanium dioxide, triacetin, D&C yellow 10 aluminum lake, polysorbate 80, and FD&C yellow 6 aluminum lake.

Manufactured for: Corcept Therapeutics Incorporated, Menlo Park, CA 94025

KORLYM® is a registered trademark of Corcept Therapeutics Incorporated.

K-00004 MAY 2017

For more information, go to www.korlym.com or www.corcept.com or call 1-855-456-7596.

This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised: 05/2017

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/627,359	Filing Date 06/19/2017	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **07/18/2018**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 30	Minus	** 30	= 0	X $50 =	0
Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $230 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
William Phillips

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Joseph K. Belanoff	Nonprovisional Application Number (if known):	15/627,359
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☐ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☑ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Kenneth A. Weber/	Date 2018-08-28
Name (Print/Typed) Kenneth A. Weber	Practitioner Registration Number 31677

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	15627359
Filing Date:	19-Jun-2017
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Filer:	Kenneth A. Weber/Jo Ann Honcik Dallara
Attorney Docket Number:	085178-1053027-011410US

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
REQUEST FOR PRIORITIZED EXAMINATION	2817	1	2000	2000
Pages:				
Claims:				
Miscellaneous-Filing:				
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2070**

Electronic Acknowledgement Receipt

EFS ID:	33560421
Application Number:	15627359
International Application Number:	
Confirmation Number:	2957
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	144579
Filer:	Kenneth A. Weber/Jo Ann Honcik Dallara
Filer Authorized By:	Kenneth A. Weber
Attorney Docket Number:	085178-1053027-011410US
Receipt Date:	28-AUG-2018
Filing Date:	19-JUN-2017
Time Stamp:	14:03:10
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$2070
RAM confirmation Number	082918INTEFSW14043400
Deposit Account	201430
Authorized User	IP eFiling

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	TrackOne Request	Track1_aia0424_RCEpreviously filed_1053027.PDF	124976 572baf8b5c02c177bc5286217b37dfdfca749b5f	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	36204 e1353c71a3c41365d243215a05427fdeb067473c	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	161180		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on September 14, 2018.

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Jo Ann Honcik Dallara/
Jo Ann Honcik Dallara

PATENT
Attorney Docket No.: 085178-1053027-011410US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Joseph K. Belanoff
Application No.: 15/627,359
Filed: Jun 19, 2017
For: CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
Customer No.: 144579

Confirmation No.: 2957
Examiner: Chris E. Simmons
Technology Center/Art Unit: 1629

AGENDA FOR INTERVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant acknowledges with gratitude the opportunity to discuss the subject application on September 18, 2018 at 3 pm EST. The following is a proposed agenda for our discussion.

AGENDA FOR INTERVIEW ON SEPTEMBER 18, 2018

I. Purpose of Interview:

1. Brief overview of the 254 pages of response filed on 7/18/18
   i. Claim amendment and response (pages 7-28)
   ii. 5 expert declarations and CVs (pages 29-122)
   iii. Exhibits 2-8 (pages 124-254)

2. Summary of prosecution strategy – to rebut and traverse PFO

3. Substantive discussion of applicant's remarks and expert declarations

II. Recommended papers to have ready access to:

Response (See pages 7-28)
Two Rule 132 declarations of Dr. Moraitis (See pages 29-41 and 56-60)

III. Prosecution strategy – Rebutting a PFO based on optimization of dosing

IV. Substantive discussion of response and declarations

1. Claim amendments – narrowing claim scope from genus to drug species – GRAs to mifepristone

2. Non-obviousness arguments

Examiner: Optimization of drug dosing is PFO unless rebutted

Applicant: The following 3 points effectively rebut the PFO

i. The prior art teaches away from invention of using doses above 300 mg/day. The additional declarations of Moriatis and Yau specifically address the Examiner's interpretation of the Korlym® Package Insert;

ii. Difference in kind versus difference of degree: FDA recommended maximum dose of 300 mg/day is not therapeutic to 87% of patients needing mifepristone to treat Cushing's syndrome.

iii. Surprising advantages – claimed invention avoids the need for clinical trials and allows patients in need the immediate benefit of the claimed combination therapy.

Respectfully submitted,

/Kenneth A. Weber/
Kenneth A. Weber
Registration No. 31,677

KILPATRICK TOWNSEND & STOCKTON LLP

Electronic Acknowledgement Receipt

EFS ID:	33730947
Application Number:	15627359
International Application Number:	
Confirmation Number:	2957
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	144579
Filer:	Kenneth A. Weber/Jo Ann Honcik Dallara
Filer Authorized By:	Kenneth A. Weber
Attorney Docket Number:	085178-1053027-011410US
Receipt Date:	14-SEP-2018
Filing Date:	19-JUN-2017
Time Stamp:	17:55:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	AgendaForInterview_1053027.pdf	102443 cacd90cc002bf0fbd90a9638b893005b94d126fc	no	2

Warnings:

Information:	
Total Files Size (in bytes):	102443

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on September 21, 2018.

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Jo Ann Honcik Dallara/
Jo Ann Honcik Dallara

PATENT
Attorney Docket No.: 085178-1053027-011410US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Joseph K. Belanoff

Application No.: 15/627,359

Filed: June 19, 2017

For: CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS

Customer No.: 144579

Confirmation No.: 2957

Examiner: Chris E. Simmons

Technology Center/Art Unit: 1629

SECOND PRELIMINARY AMENDMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Prior to examination of the above-referenced application, please enter the following amendments and consider the following remarks:

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks/Arguments begin on page 7 of this paper.

AMENDMENTS TO THE SPECIFICATION

Please replace paragraph 0048 with the following amended paragraph:

[0048] According to the U.S. Food and Drug Administration (FDA) definition ~~(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm, accessed February 16, 2017),~~ strong CYP3A inhibitors are expected to increase the AUC of other drugs by greater than five-fold. Ketoconazole is identified by the FDA as a strong CYP3A inhibitor (See FDA web posting: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers).

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings of claims in the application.

Listing of Claims:

LISTING OF CLAIMS:

1. (Currently amended) A method of treating Cushing' s syndrome in a patient who is taking a once-daily (OD) dose of mifepristone, said OD dose having an original OD dose amount of mifepristone, comprising reducing the amount of the OD dose from said original OD dose amount to an adjusted OD dose amount that is at least 33% less than said original OD dose amount when the patient is receiving concomitant administration of a CYP3A inhibitor, wherein said original OD dose amount is 900 milligrams (mg) per day or 1200 mg per day of mifepristone, and said adjusted OD dose amount is 600 mg per day of mifepristone and said CYP3A inhibitor is selected from the group consisting of: ketoconazole, itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritprevir and voriconazole.

2. (**Canceled**)

3. (Previously presented) The method of claim 1, wherein said adjusted OD dose is 600 mg per day of mifepristone, after upwardly titrating the adjusted OD dose amount from 300 mg per day up to 600 mg per day of mifepristone.

Claims 4-6. (**Canceled**)

7. (Original) The method of claim 1, wherein said CYP3A inhibitor is ketoconazole.

8. (Currently amended) The method of claim [[~~4~~]] 1, wherein said CYP3A inhibitor is ~~ketoconazole~~ itraconazole.

9. (Currently amended) The method of claim [[2]] 1, wherein said CYP3A inhibitor is ~~ketoconazole~~ clarithromycin.

10. (Currently amended) A method of treating symptoms associated with elevated cortisol levels in a patient who is taking a once-daily (OD) dose of mifepristone, said OD dose having an original OD dose amount of mifepristone, comprising reducing the amount of the OD dose from said original OD dose amount to an adjusted OD dose amount that is at least 33% less than said original OD dose amount when the patient is receiving concomitant administration of a CYP3A inhibitor, wherein said original OD dose amount is 900 milligrams (mg) per day or 1200 mg per day of mifepristone, and said adjusted OD dose amount is 600 mg per day of mifepristone and said CYP3A inhibitor is selected from the group consisting of: ketoconazole, itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritprevir and voriconazole.

.

11. **(Canceled)**

12. (Previously presented) The method of claim 10, wherein said adjusted OD dose amount is 600 mg per day of mifepristone, after upwardly titrating the adjusted OD dose amount from 300 mg per day up to 600 mg per day of mifepristone.

13. (Currently amended) The method of claim 12, wherein said CYP3A inhibitor is itraconazole ~~a strong CYP3A inhibitor~~.

Claims 14-15. **(Canceled)**

16. (Previously presented) The method of claim 10, wherein said CYP3A inhibitor is ketoconazole.

17. (Currently amended) The method of claim [[13]] 10, wherein said CYP3A inhibitor is ~~ketoconazole~~ clarithromycin.

18. (Currently amended) The method of claim [[11]] 10, wherein said CYP3A inhibitor is ~~ketoconazole~~ itraconazole.

19. (Currently amended) A method of controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome who is taking a once-daily (OD) dose of mifepristone, said OD dose having an original OD dose amount of mifepristone, comprising reducing the amount of the OD dose from said original OD dose amount to an adjusted OD dose amount that is at least 33% less than said original OD dose amount when the patient is receiving concomitant administration of a CYP3A inhibitor, wherein said original OD dose amount is 900 milligrams (mg) per day or 1200 mg per day of mifepristone, and said adjusted OD dose amount is 600 mg per day of mifepristone and said CYP3A inhibitor is selected from the group consisting of: ketoconazole, itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritprevir and voriconazole.

20. (**Canceled**)

21. (Previously presented) The method of claim 19, wherein said adjusted OD dose is 600 mg per day of mifepristone after upwardly titrating the adjusted OD dose amount from 300 mg per day up to 600 mg per day of mifepristone.

Claims 22-24. (**Canceled**)

25. (Original) The method of claim 19, wherein said CYP3A inhibitor is ketoconazole.

26. (Currently amended) The method of claim [[22]] 19, wherein said CYP3A inhibitor is ~~ketoconazole~~ itraconazole.

27. (Currently amended) The method of claim [[20]] 19, wherein said CYP3A inhibitor is ~~ketoconazole~~ clarithromycin.

28. (Currently amended) A method of controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome, wherein said patient is taking a once daily (OD) dose of mifepristone, said OD dose having an OD dose amount of 900 milligrams (mg) or 1200 mg mifepristone, comprising reducing the OD amount of mifepristone to provide a reduced OD dose of 600 mg mifepristone, and administering a said reduced OD dose of 600 milligrams (mg) mifepristone when the patient is receiving concomitant administration of a CYP3A inhibitor selected from the group consisting of: ketoconazole, itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritprevir and voriconazole.

29. (Original) The method of claim 28, wherein said CYP3A inhibitor is ketoconazole.

30. (Previously presented) The method of claim 29, wherein said reduced OD dose of 600 mg mifepristone per day is titrated up to 600 mg mifepristone per day at least two days after administering at least two reduced OD doses of 300 mg mifepristone per day.

REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 1, 3, 7-10, 12, 16-19, 21 and 25-30 will be pending in this application. Claims 1, 8-10, 13, 17-19 and 26-28 have been amended. Claims 2, 4-6, 11, 14-15, 20 and 22-24 have been canceled, and no new claims have been added.

No new matter is added. Independent claims 1, 10, 19 and 28 have been amended to include the CYP3A inhibitors of claim 5, 6, 23 and 24. The independent claims have also been amended to recite additional drugs, cobicistat, tipranivir. paritprevir and troleandomycin which find support at ¶7. The amendments to claims 8-9, 13, 17-18 and 26-27 are amended to recite specific drugs which find support from original claim 1.

Pursuant to Rule 133(b), applicant acknowledges with gratitude the Examiner's time and thoughts during the interview of September 20, 2018. No agreement was reached but the examiner indicated that the arguments and amendments previously presented should move the case along to allowance with additional amendments and presentation of evidence.

It is the purpose of this second Preliminary Amendment to address the issues raised by the Examiner during the interview.

1. The internet link on paragraph 48 is deleted.

2. Evidence that the CYP3A inhibitors of claim 6 were considered strong inhibitors by the FDA.

During the interview, Examiner Simmons suggested that applicant amend the independent claims to recite specific CYP3A inhibitors and asked if the list in claim 6 are all strong inhibitors. The original list was ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saguinavir, telaprevir, telithromycin, and voriconazole.

The following drugs are now deleted from the list: fluconazole, cimetidine, atazanavir, amprenavir, fosamprenavir, and telithromycin. Four additional drugs were added cobicistat and troleandomycin, tipranavir, and paritaprevir. These drugs are recited in paragraph 7 of the originally filed application. The drugs recited by the independent claims are all considered by the FDA as strong inhibitors of CYP3A. See Table 3-2 on the FDA website: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Table 3-2: Examples of clinical inhibitors for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling) (9/26/2016)

	Strong inhibitors	Moderate inhibitors	Weak inhibitors
CYP1A2	ciprofloxacin, enoxacin, fluvoxamine[m], zafirlukast	methoxsalen, mexiletine ,oral contraceptives	acyclovir, allopurinol, cimetidine, peginterferon alpha-2a, piperine, zileuton
CYP2B6	-	-	clopidogrel[b], ticlopidine [b], voriconazole[c]
CYP2C8	clopidogrel[b], gemfibrozil[c]	deferasirox, teriflunomide	telithromycin, trimethoprim
CYP2C9	-	amiodarone, felbamate, fluconazole[d], miconazole, piperine	diosmin, disulfiram, fluvastatin, fluvoxamine[m], voriconazole
CYP2C19	fluconazole[d], fluoxetine[m], fluvoxamine[m], ticlopidine	-	omeprazole, voriconazole
CYP2D6	bupropion, fluoxetine[m], paroxetine, quinidine[m], terbinafine	cimetidine, cinacalcet, duloxetine, fluvoxamine[m], mirabegron	abiraterone, amiodarone, celecoxib, cimetidine, clobazam, cobicistat, desvenlafaxine, escitalopram, labetalol, lorcaserin, ritonavir[n,o], sertraline, vemurafenib
CYP3A	boceprevir, cobicistat[m], conivaptan [m], danoprevir and ritonavir[o], elvitegravir and ritonavir[o], grapefruit juice[k], indinavir and ritonavir[o], itraconazole[c], ketoconazole, lopinavir and ritonavir[o,q], paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)[o], posaconazole, ritonavir[h,j], saquinavir and ritonavir[o,q], telaprevir[m], tipranavir and ritonavir[o,q], troleandomycin, voriconazole clarithromycin[m], diltiazem[m], idelalisib, nefazodone, nelfinavir[m]	aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone[m], erythromycin, fluconazole[d], fluvoxamine[m], imatinib, tofisopam, verapamil[m]	chloroxazone, cilostazol, fosaprepitant, istradefylline, ivacaftor[m], lomitapide, ranitidine, ranolazine[m], tacrolimus, ticagrelor [m]

3. A terminal disclaimer in view of USSN 15/627,368 has been filed.

4. During the interview, both the Examiner and applicant's attorney noted that dependent claims 3, 12, 21 and 30 read on 300 mg/day. There was a discussion regarding the scope of these four claims. We considered canceling these claims.

On reflection, it appears that these claims embrace the inventive concepts of the independent claims because they require the combination of FDA precluded high doses of mifepristone when combined with strong CYP3A inhibitors. The limitation of these dependent claims requires that the patient begin dosing with mifepristone at the 2012 FDA accepted dose of 300 mgs/day before being administered the higher doses that define the inventive elements of the claims. That is, dependent claims 3, 12, 21, and 30 all require titration up to 600 mg/day when the patient is receiving concomitant administration of a CYP3A inhibitor. In view of this understanding, it is submitted that the claims 3, 12, 21 and 30 are appropriately limited. If the independent claims are non-obvious over the prior art then these dependent claims should also be considered non-obvious.

5. Attachment A identified in the Preliminary Amendment filed on July 19, 2018 was advertently omitted. Attachment A is Morgan and Laufgraben (2013) and is properly attached to this paper. The relevant portion of the article is found at the 2nd column on page 327. The authors wrote:

> *Dosing and Administration*
>
> Mifepristone should be administered as a once-daily oral dose with food and should be taken this way consistently to avoid changes in plasma concentrations. The starting dosage is 300 mg/day, which may be escalated by 300 mg every 2–4 weeks, not to exceed a dosage of 1200 mg/day or 20 mg/kg/day. The maximum dosage for patients with renal or mild-to-moderate hepatic impairment should be 600 mg/day. If used with a CYP3A inhibitor, the maximum dose should not exceed 300 mg/day.[18] Dosing recommendations are based on the most recent multicenter trial data.[37]

6. We had discussed including a 900 mg dose in the independent claim. That is not included in this application and is pursued in the related application, USSN 15/627,368.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this application are in condition for examination.

Except for the issue fees payable under 37 C.F.R. § 1.18, the Director is authorized to charge any additional fees during pendency of this application, including any required extension of time fees, or credit any overpayment to Deposit Account Number 20-1430. This paragraph is intended to be a constructive petition for extension of time in accordance with 37 C.F.R. § 1.136(a)(3).

If the Examiner believes a telephone conference would expedite prosecution of this application, please contact the undersigned at (415) 576-0200 or KWeber@KilpatrickTownsend.com.

Respectfully submitted,

/Kenneth A. Weber/
Kenneth A. Weber
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KILPATRICK TOWNSEND & STOCKTON LLP

Attachment: A. Morgan and Laufgraber (2013), Mifepristone for Management of Cushing's Syndome, *Pharmacotherapy*, Vol 33:3 319-329.

ATTACHMENT A

Mifepristone for Management of Cushing's Syndrome

Farah H. Morgan, and Marc J. Laufgraben

Cushing's syndrome is a debilitating endocrine disorder caused by elevated circulating glucocorticoid levels. Although uncommon, Cushing's syndrome is associated with significant morbidity necessitating rapid reversal of hypercortisolemia. Primary therapy for most patients with Cushing's syndrome is surgical, but many patients will require additional treatments with radiation or drugs. Although several options for drug therapy exist, few are readily available and all have dose-limiting adverse effects. Mifepristone (RU 486), a first-in-class glucocorticoid receptor antagonist, was approved by the United States Food and Drug Administration in 2012 for use in Cushing's syndrome to control hyperglycemia in patients who are not surgical candidates or have not achieved remission from surgery. The drug is approved for oral once-daily administration. In its pivotal trial, 60% of patients responded to mifepristone with significant improvements in glycemic control and 38% had a reduction in diastolic blood pressure. The most common adverse events were nausea, fatigue, headache, endometrial hyperplasia, and hypokalemia. Adrenal insufficiency occurred in fewer than 5% of patients. The recommended starting dosage of mifepristone is 300 mg/day. The dosage may be increased every 2–4 weeks up to a maximum of 1200 mg/day, although it should not exceed 20 mg/kg/day. Significant drug–drug interactions exist due to mifepristone's effects on a number of cytochrome P450 enzymes. Despite its limitations, mifepristone is a welcome addition and an appropriate alternative to the available drug therapy for Cushing's syndrome.

Key Words: mifepristone, glucocorticoid receptor antagonist, Cushing's syndrome, Cushing's disease, RU486.

(Pharmacotherapy 2013;33(3):319–329)

Cushing's syndrome is a rare but debilitating endocrine disorder caused by excess circulating glucocorticoids. The excess glucocorticoids result from increased glucocorticoid production in the adrenal gland secondary to adrenal stimulation or a primary adrenal tumor. For most forms of Cushing's syndrome, the initial treatment is surgical. However, a substantial proportion of patients will not be cured by surgery. Second-line therapy can include additional surgery, radiation, or pharmacologic agents. Previously available drugs have primarily been inhibitors of adrenal steroid synthesis, and the use of these agents has been limited by availability and tolerability. Mifepristone, a first-in-class glucocorticoid receptor antagonist, was approved by the United States Food and Drug Administration (FDA) in 2012 for use in patients with hyperglycemia secondary to Cushing's syndrome. With approval of this new agent, practitioners need a thorough understanding of its

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pharmacology, pharmacokinetics, pharmacodynamics, clinical efficacy, indications for use, and limitations.

Cortisol: Normal Physiology

Secretion of cortisol is maintained by a classic endocrine feedback system. Cortisol production occurs in the zona fasciculata cells of the adrenal cortex. These cells are stimulated by adrenocorticotrophic hormone (ACTH), which is secreted by corticotroph cells in the anterior pituitary gland. ACTH production is stimulated by corticotrophin-releasing hormone (CRH) produced in the paraventricular nucleus of the hypothalamus. Circulating cortisol then provides negative feedback to inhibit production of CRH and ACTH. Thus, cortisol dynamics depend on normal hypothalamic, pituitary, and adrenal function—the hypothalamic-pituitary-adrenal axis (Figure 1). Normal cortisol levels follow a circadian rhythm with a peak in the early morning (7:00–9:00 A.M.) and a nadir at 11:00 P.M. CRH production is further regulated by physiologic and emotional stress.[1]

Cortisol is necessary to sustain life. It plays a role in multiple essential functions including carbohydrate, protein, and lipid metabolism and vascular tone and blood pressure maintenance. It is also involved in the immune system and responses to stress. Glucocorticoids exert their actions mainly through binding at the glucocorticoid receptor, a member of the thyroid and steroid hormone receptor superfamily of nuclear transcription factors. As would be expected, the glucocorticoid receptor is expressed widely in peripheral tissues and brain regions. Many glucocorticoids, including cortisol, also have affinity for the mineralocorticoid receptor. However, under normal circumstances, the renal mineralocorticoid receptor is "protected" from cortisol binding by the local activity of type 2 11β-hydroxysteroid dehydrogenase (11β-HSD), which converts cortisol to cortisone and does not bind to the mineralocorticoid receptor. Under physiologic circumstances, aldosterone is the primary activator of the mineralocorticoid receptor; its activation promotes sodium retention (and therefore maintenance of blood pressure) and potassium excretion.[1, 2]

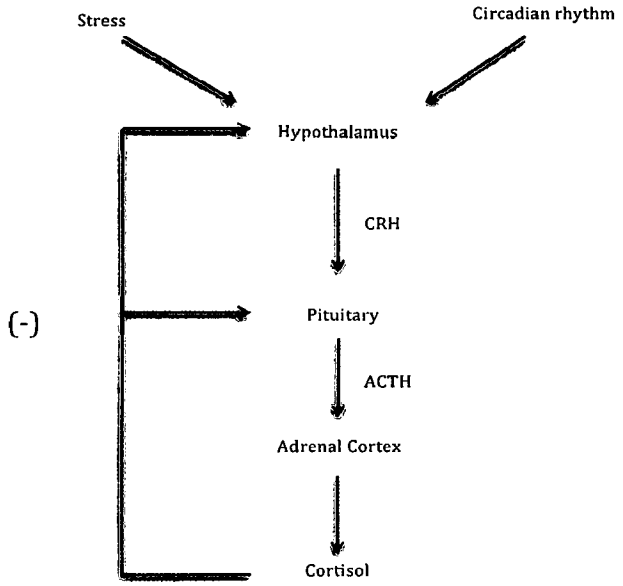

Figure 1. Normal regulation of the hypothalamic-pituitary-adrenocortical axis.[1, 2] ACTH = andrenocorticotrophic hormone; CRH = corticotrophin-releasing hormone.

Deficiency of cortisol results in the signs and symptoms of adrenal insufficiency, which can vary in severity from fatigue and anorexia to hypotension and hypoglycemia to shock and death. Cortisol excess results in Cushing's syndrome.

Cushing's Syndrome

Cushing's syndrome is the result of excess circulating glucocorticoids. Exogenous, or iatrogenic, Cushing's syndrome is common and typically results from the use of supraphysiologic doses of glucocorticoids to treat pulmonary, rheumatologic, hematologic, or other disorders. Endogenous Cushing's syndrome is rare and results from inappropriate activation of either the pituitary gland or adrenal glands, leading to increased circulating cortisol levels. The majority of cases are caused by an ACTH-secreting tumor of the pituitary gland (i.e., Cushing's disease). Cushing's syndrome may also result from ectopic secretion of ACTH by neoplasms such as small cell lung cancer and carcinoid tumors; rarely, a tumor may secrete CRH. Cushing's syndrome can also result from benign, malignant, or hyperplastic diseases of the adrenal glands that secrete cortisol in the absence of ACTH stimulation.[3–5]

The excess cortisol seen in Cushing's syndrome results in hypertension, hyperglycemia, obesity, and a myriad of other problems (Table 1).[5] These complications lead to significant morbidity related to illness and twice the mortality rate in patients with Cushing's syndrome compared to the general population.[6] Diabetes mellitus and hypertension are the most

Table 1. Signs and Symptoms of Cushing's Syndrome[5]

Symptoms	Signs	Other Conditions
Depression	Obesity (especially central obesity)	Hypokalemia
Fatigue	Facial plethora	Hypertension
Weight gain	Moon facies	Diabetes mellitus
Irregular menses	Easy bruising	Osteoporosis
Back pain	Striae (especially wide violaceous striae)	Renal calculi
Insomnia	Proximal myopathy	
Muscle weakness	Dorsocervical fat pad	
Irritability	Supraclavicular fat pads	
	Edema	
	Acne	
	Thin skin	
	Hirsutism	
	Female balding	

important predictors of death.[6] Hypertension occurs in 80% of patients with Cushing's syndrome and is thought to be caused by the effect of cortisol on both the glucocorticoid receptor and the mineralocorticoid receptor.[4] The excess cortisol overwhelms the ability of type 2 11β-HSD to convert it to cortisone, and thus cortisol has access to and activates the mineralocorticoid receptor. Impaired glucose tolerance or type 2 diabetes also occurs in 80% of patients as a result of increased insulin resistance and impaired insulin secretion.[6] Glucocorticoids increase insulin resistance through actions on liver, skeletal muscle, and adipose tissue. The net result of increased liver gluconeogenesis and decreased glucose uptake in skeletal muscle and adipose tissue is hyperglycemia.[6] Impaired insulin secretion also occurs as a result of glucocorticoids binding to pancreatic β cells, resulting in impaired β-cell function.[6] This combined effect causes hyperglycemia that can be very difficult to treat, often requiring escalating doses of insulin for appropriate management.

Diagnosis of Cushing's Syndrome

Because of the complexity of the screening and diagnostic algorithms for Cushing's syndrome, referral to an endocrinologist is appropriate when the disorder is suspected. Accurate diagnosis of Cushing's syndrome is critical to avoid unnecessary testing, procedures, and expenditures.[5, 7]

Before considering biochemical testing for endogenous Cushing's syndrome, it is important to rule out exogenous glucocorticoid exposure causing iatrogenic Cushing's syndrome. Initial testing can include measurement of 24-hour urine free cortisol, late-night salivary cortisol collected at 11:00 P.M. or 12:00 A.M., or early morning cortisol after dexamethasone 1 mg the previous evening at 11:00 P.M. (overnight dexamethasone 1-mg suppression test). When an abnormal result is obtained, a physiologic cause of hypercortisolemia, such as depression or other psychiatric illness, alcohol abuse, physical stress, malnutrition, or pregnancy, should be excluded.[5, 8, 9]

After establishment of the diagnosis of Cushing's syndrome, the endocrinologist must determine the source of the hypercortisolemia. A low or undetectable ACTH level should raise the suspicion for an ACTH-independent source, and imaging of the adrenal glands should be performed. An elevated or nonsuppressed ("inappropriately normal") ACTH level reflects an ACTH-dependent source of hypercortisolemia. A combination of noninvasive biochemical testing (high-dose dexamethasone testing or CRH stimulation), pituitary magnetic resonance imaging, and, often, inferior petrosal sinus sampling for ACTH may be necessary to determine if the source is an ACTH-secreting pituitary adenoma or a nonpituitary tumor with ectopic ACTH production.[5, 10]

Treatment Options for Cushing's Syndrome

Treatment of Cushing's syndrome is dependent on the identified source of the disorder. Patients with cortisol-secreting adrenal adenomas are usually cured with unilateral adrenalectomy, whereas patients with adrenocortical carcinoma often have persistent or recurrent disease after surgery due to local invasion or metastases. In patients with the ectopic ACTH syndrome, initial treatment is directed at the underlying neoplasm. Medical therapies are often needed in patients with persistent hypercortisolemia.

In patients with Cushing's disease (ACTH-secreting pituitary adenomas), who make up the majority of patients with Cushing's syndrome, the primary treatment modality is transsphenoidal surgery, which results in remission rates of 50–80%.[3, 11–14] If there is failure to attain remission after initial surgery or if the disease recurs later, second-line interventions include repeat surgery, radiotherapy, bilateral adrenalectomy, or pharmacologic therapy.[3, 13, 15]

Medical therapy for hypercortisolemia is provided to patients who are unable to undergo surgery because of another illness, to patients

who have failed to achieve remission with other treatment modalities, as a bridge to radiotherapy or surgery, or as a palliative option. A number of potential targets exist for medical therapy, including inhibition of steroidogenesis, inhibition of ACTH secretion, and steroid receptor antagonism. The most commonly used agents are steroidogenesis inhibitors such as ketoconazole, metyrapone, and mitotane. Other agents in this class include aminoglutethimide and etomidate (Table 2).[3, 13, 16–20]

Steroidogenesis inhibitors are considered adrenal-directed medical therapy because they control cortisol production by directly decreasing adrenal hormone production. Ketoconazole is the most commonly used steroidogenesis inhibitor because of its availability and relatively rapid onset of action. Ketoconazole was developed as an antifungal drug. It inhibits cortisol synthesis by preventing cholesterol side chain cleavage, inhibiting cytochrome P450 enzyme 17,20-lyase, and inhibiting 11β-hydroxylase, the enzyme involved in the final step of cortisol synthesis. Its major limiting adverse effect is elevated liver enzyme levels, which occur in up to 10% of patients. It can also cause hypogonadism in men because of inhibition of testosterone synthesis.[16, 19–21]

Metyrapone blocks the production of cortisol through inhibition of 11β-hydroxylase. This effectively reduces hypercortisolemia, but because metyrapone is specific for a single enzyme late in the steroid biosynthesis pathway, there is often a dramatic rise in steroids formed proximal to 11β-hydroxylase, particularly 11-deoxycortisol, a mineralocorticoid that causes the frequent adverse effects of hypokalemia, edema, and hypertension. An increase in adrenal androgens can cause hirsutism in women. In an effort to limit the accumulation of precursor steroids, metyrapone is often used in combination with other medical therapies such as ketoconazole. It is currently available in the United States directly from the manufacturer.[16, 19, 20, 22]

Mitotane is used most often for the management of adrenocortical carcinoma. It works through the inhibition of multiple enzymes[19] and, unlike other agents, is directly cytotoxic to adrenocortical cells. Undesirable features of mitotane are its delayed onset of action and dose-limiting gastrointestinal effects. Serious neurologic effects, including ataxia, vertigo, and confusion, also occur at higher doses. These adverse effects limit the tolerability of mitotane,

Table 2. Drug Therapy for the Treatment of Cushing's Syndrome[3, 13, 16-20]

Drug	Dose Range	Mechanism of Action/Site of Action	Adverse Reactions	Comments
Ketoconazole	200 mg b.i.d.–400 mg t.i.d.	Inhibition of cortisol synthesis: 11β-hydroxlase, 17-hydroxylase, and C17, 20 lyse	Hepatotoxicity, hypogonadism	Drug interactions due to inhibition of CYP3A
Metyrapone	250–1500 mg q.i.d.	Inhibition of cortisol synthesis: 11β-hydroxylase	Hypertension, edema, hypokalemia, hirsutism	Limited availability, often combined with another agent
Mitotane	500–3000 mg t.i.d.	Inhibition of cortisol synthesis: 11β-hydroxylase and cholesterol side chains	Gastrointestinal effects, ataxia, confusion	Slow onset
Aminoglutethimide	250 mg b.i.d.–2000 mg q.i.d.	Inhibition of cortisol synthesis and side chain cleavage: 11β-hydroxylase and 18 hydroxylase	Rash, fever, dizziness, depression	Limited availability and efficacy
Etomidate	0.1–0.3 mg/kg/hr	Inhibition of cortisol synthesis: 11b-hydroxylase, 17 hydroxylase, and C17, 20 lyse	Sedation	Intravenous administration only
Bromocriptine	2.5–40 mg/day	Dopamine agonist	Nausea, hypotension	Limited efficacy
Cabergoline	1–2 mg/wk	Dopamine agonist	Nausea, hypotension	Limited efficacy
Pasireotide	600–900 μg b.i.d.	Somatostatin analog, somatostatin type 5 receptors	Hyperglycemia	In phase III trials
Mifepristone	300–1200 mg/day	Glucocorticoid receptor antagonism	Hypokalemia, adrenal insufficiency, endometrial hyperplasia, nausea	Expensive, difficult to monitor therapy

CYP = cytochrome P450.

and it must often be used in combination with another drug to attain more rapid control of hypercortisolemia.[3, 19, 23]

Aminoglutethimide and etomidate are steroidogenesis inhibitors that are used infrequently due to their limitations. Aminoglutethimide, which works by inhibiting the conversion of cholesterol to pregnenolone, is neither particularly effective as monotherapy nor readily available in the United States.[16, 19] Etomidate, an intravenous agent used for anesthesia induction, inhibits cholesterol side chain cleavage and 11β-hydroxylase. It has been used in emergent settings for the rapid control of hypercortisolemia but is not practical for routine use due to its sedative effects.[16, 19, 24]

Drugs that suppress ACTH secretion have been investigated for use in the management of Cushing's disease. Among these are dopamine agonists and somatostatin analogs. Dopamine agonists are potentially attractive agents for the treatment of Cushing's syndrome because of the potential for decreased prevalence of glucose intolerance and diabetes,[6, 13, 16, 25] but results have been variable and few patients with Cushing's syndrome experienced sustained improvement after receiving dopamine agonist therapy.[13, 19, 20] Bromocriptine causes an acute decrease in ACTH, although this effect is not sustained over time with repeated dosing.

Octreotide, a somatostatin analog that predominantly acts on type 2 somatostatin receptors, is largely ineffective in lowering ACTH levels.[13, 16] A newer multiligand somatostatin analog, pasireotide (SOM230), has been demonstrated to inhibit ACTH release in human corticotroph cells through interaction with type 5 somatostatin receptors.[6, 16, 26] Its use has resulted in reduced urine free cortisol levels and improved features of Cushing's syndrome in phase II and III studies, but it appears to have the undesirable effect of hyperglycemia,[17, 27] possibly caused by direct inhibition of insulin and incretin hormone secretion.

Mifepristone

Mifepristone (RU486), a derivative of the synthetic progestin norethindrone, was discovered in the 1980s at the French pharmaceutical company Roussel-Uclaf as part of a special research project to develop antiglucocorticoid compounds.[28] Its antiprogestin effects were quickly recognized, and it was developed as an abortifacient because of its effectiveness in pregnancy termination, particularly when combined with a prostaglandin. Other investigated uses that take advantage of its antiprogesterone activity include the treatment of meningioma and breast cancer. Unfortunately, research on mifepristone has been hindered by the controversy surrounding its use as an abortion pill.[28]

Mifepristone is a selective antagonist of the progesterone receptor at lower doses and blocks the glucocorticoid receptor at higher doses.[18] Mifepristone occupies glucocorticoid receptors with an affinity that is 4-fold higher than that of dexamethasone and 18-fold higher than that of cortisol.[28] After binding, it inhibits transcriptional activation of the glucocorticoid receptor, thereby decreasing the physiologic effects of hypercortisolemia. It blocks both central (negative feedback on CRH and ACTH) and peripheral actions of cortisol.[28] Antagonism of negative feedback of cortisol results in increased circulating ACTH and cortisol levels.[28, 29] It has little affinity for the mineralocorticoid receptor and estrogen receptors but is a weak antiandrogen. Mifepristone is also a weak glucocorticoid agonist, roughly 1/250th of that of cortisol, although this weak effect is unlikely to prevent adrenal insufficiency.[28–30]

Pharmacokinetics and Pharmacodynamics

Mifepristone is readily absorbed after oral ingestion with a bioavailability exceeding 30%.[31] Time to peak plasma concentrations after oral administration of a single dose is 1–2 hours, increasing to 1–4 hours with repeated doses. Food increases the plasma concentrations of mifepristone. Mifepristone has three active metabolites, all of which have high affinity and antagonism for the glucocorticoid receptor (~50% of that of mifepristone). Cytochrome P450 (CYP) 3A is involved in the metabolism of mifepristone. Two of the known active metabolites are a result of demethylation, whereas the third is a result of hydroxylation. Mean plasma concentration of these metabolites peaks between 2 and 8 hours after multiple doses of the drug and eventually exceeds that of mifepristone.[18] Therefore, drug interactions affecting enzyme metabolism may affect the degree of antagonism of the glucocorticoid receptor. Time to steady state with repeated daily dosing is 2 weeks. Mifepristone has a very long elimination half-life of 85 hours after repeated dosing.[18]

Significant drug–drug interactions exist because of mifepristone's effects on several CYP

enzymes. For example, CYP3A is involved in the metabolism of mifepristone and mifepristone also both inhibits and induces CYP3A. Therefore, drugs that are metabolized by CYP3A should be avoided or used with caution (Table 3). When a once-daily dose of mifepristone 1200 mg was coadministered with simvastatin 80 mg for 10 days in healthy volunteers, there was an 18-fold increase in the maximum plasma concentration (C_{max}) of simvastatin acid and a 7-fold increase in the C_{max} of simvastatin, significantly increasing the risk of toxicity of this drug.[18] Drugs that inhibit CYP3A can increase mifepristone levels, and a dose reduction of mifepristone may be required (Table 3). Coadministration of mifepristone and CYP3A inducers has not been studied. Other enzymes affected by mifepristone are CYP2C8/2C9 and CYP2B6. Drugs metabolized by these pathways should be used with caution (Table 4). The C_{max} of fluvastatin 40 mg was increased 1.76-fold when coadministered with mifepristone 1200 mg.[18] Because of the long half-life of mifepristone and time to reach steady state, dosage adjustment of drugs with potential interactions should not occur more frequently than every 2 weeks. Drugs that are contraindicated for use with mifepristone can be safely initiated 2 weeks after the discontinuation of mifepristone.[18]

Mean exposure (plasma concentration over time) to mifepristone (evaluated with multiple 1200-mg doses for 7 days) increased by 31% in patients with a creatinine clearance less than 30 ml/min compared to patients with normal renal function (creatinine clearance > 60 ml/min). There was large variability among subjects in the exposure of mifepristone and its metabolites. The pharmacokinetics of mifepristone in patients with moderate hepatic impairment was found to be similar to that in patients with normal hepatic function. The pharmacokinetics in patients with severe hepatic impairment has not been studied.[18]

Table 4. Drugs that Interact with Mifepristone Through CYP2C8/2C9 and CYP2B6[18]

Drugs Metabolized by CYP2C8/2C9	Drugs Metabolized by CYP2B6
Use lowest dose and monitor closely	Not studied—use lowest dose
Fluvastatin	Bupropion
NSAIDs	Efavirenz
Warfarin	
Repaglinide	

CYP = cytochrome P450; NSAIDs = nonsteroidal anti-inflammatory drugs.

Clinical Efficacy

Initial information regarding efficacy of mifepristone for use in Cushing's syndrome came from case reports. In 1985, a patient with Cushing's syndrome secondary to ectopic ACTH secretion was treated with mifepristone.[32] The initial dosage was 5 mg/kg/day because it was known that a dosage of 6 mg/kg/day prevents morning adrenal suppression from dexamethasone 1 mg. The dosage was increased in 5-mg/kg/day increments every 1–2 days to a maximum of 20 mg/kg/day. Treatment resulted in resolution of clinical effects of Cushing's syndrome, redistribution of fat, and improvement in hyperglycemia and

Table 3. Sample List of Drugs or Foods that Interact with Mifepristone Through CYP4503A[18]

Drugs Metabolized by CYP3A	CYP3A Inhibitors	CYP3A Inducers
Use alternative drug or administer lowest dose and/or decrease frequency	Limit mifepristone to 300 mg/day	Do not use (has not been studied)
Cyclosporine	Azole antifungals	Rifabutin
Dihydroergotamine	Protease inhibitors	Phenobarbital
Ergotamine	Macrolides	Phenytoin
Fentanyl	Mibefradil	Carbamazepine
Pimozide	Nefazodone	St. John's wort
Quinidine	Conivaptan	Rifampin
Sirolimus	Caution—use lowest effective dose of mifepristone	
Tacrolimus	Imatinib	
Simvastatin	Aprepitant	
Lovastatin	Ciprofloxacin	
	Grapefruit juice	
	Nondihydropyridine CCBs	

CCBs = calcium channel blockers; CYP = cytochrome P450.

hypertension. Fasting glucose and 2-hour glucose levels after ingestion of glucose 100 g normalized with the highest doses. In contrast, levels of ACTH, serum cortisol, and urine free cortisol remained elevated. Treatment was stopped because of the limited availability of mifepristone.

A cases series of 10 patients with Cushing's syndrome treated with mifepristone was published in 1989.[28, 33, 34] Six of the 10 patients who received mifepristone 5–22 mg/kg/day had their symptoms of hypercortisolemia alleviated. Patients' hypertension improved, with reduction in mean blood pressure. Carbohydrate metabolism also improved, as evidenced by reduction in 2-hour plasma glucose levels during oral glucose tolerance testing. Two of three men complained of gynecomastia and impotence, whereas only two patients developed adrenal insufficiency.[34]

Subsequent studies ensued to elucidate the drug's antiglucocorticoid effects and relative safety for long-term treatment. In 1994, mifepristone 200 mg/day was administered to 10 healthy volunteers for 8 consecutive days. The investigators found heightened activation of the hypothalamic-pituitary-adrenal axis with elevations in plasma cortisol, urinary cortisol, and ACTH levels, although there was no evidence of clinical symptoms. Adrenocortical reserves seemed to be preserved as evidenced by the ability to further increase circulating cortisol with ACTH stimulation.[29] In 1995, the antiglucocorticoid effects of mifepristone were evaluated in eight healthy men.[35] This study evaluated subjects during the infusion of cortisol after the ingestion of mifepristone 600 mg or placebo and during the infusion of normal saline with placebo or mifepristone. The increase in plasma glucose levels seen with cortisol infusion plus placebo was not demonstrated when cortisol was administered after mifepristone ingestion. Although this study involved only healthy men and was limited by the small number of patients studied, it supported the concept that mifepristone may suppress the effects of hypercortisolemia on glucose.

In 2009, results from a retrospective study were published: 20 patients with Cushing's syndrome due to malignant or benign causes were treated with oral mifepristone 400–2000 mg/day for 5 days to 24 months.[36] The median initiation dose was 400 mg with a median maximum dose of 600 mg/day. Eight of the 12 patients with adrenocortical carcinoma, most of whom had failed surgery, cytotoxic chemotherapy, and/or mitotane as well as other drug therapy, had rapid improvement within the first month of initiation of mifepristone. Seven of these 12 patients developed hypokalemia, although this required cessation of therapy in only 1 patient. All three patients with ectopic ACTH secretion had improvement in clinical symptoms, and the two patients with diabetes required a rapid decrease in their insulin dose. Three of four patients with Cushing's disease had improvement in clinical signs of hypercortisolemia; levels of ACTH and cortisol increased in all four patients. The last patient treated had bilateral adrenal hyperplasia. Hypertension and signs of hypercortisolemia improved within 3 months of therapy, and hemoglobin A_{1c} (A1C) was reduced from 7.1% to 6.4%. Overall, the investigators found improvement in clinical symptoms in 15 of the 20 patients along with improvement in blood glucose levels in 4 of 7 patients with hyperglycemia. Serious adverse effects included signs of adrenal insufficiency in 3 patients and hypokalemia in 11 patients.

Recently, an open-label, 24-week, multicenter clinical study evaluated safety and efficacy of mifepristone for the treatment of Cushing's syndrome; the results led to the drug's approval by the FDA in 2012.[37] A separate open-label extension of this trial is ongoing. The study enrolled 50 patients with continued biochemical and clinical evidence of hypercortisolemia after failed multimodality therapy, largely with surgery and/or radiotherapy. Endogenous hypercortisolemia was defined as elevated urine free cortisol levels measured from at least two 24-hour collections and elevated late-night salivary cortisol levels and/or lack of suppression with dexamethasone. Inclusion criteria were associated type 2 diabetes, impaired glucose tolerance diagnosed from an oral glucose tolerance test, or hypertension with at least two other signs or symptoms of Cushing's syndrome. Exclusion criteria included an A1C greater than 11%, poorly controlled hypertension (blood pressure > 170/110 mm Hg), use of drugs to treat hypercortisolemia within 1 month, uncorrected hypokalemia, and uncontrolled thyroid disease. Women with evidence of endometrial hyperplasia, cancer, or polyps and those with an intact uterus who required anticoagulation or had hemorrhagic disorders were also excluded. Initiation or additions to therapy for diabetes, impaired glucose tolerance, depression, hyperlipidemia, or hypertension were not allowed, with the exception of the addition of a mineralocorticoid antagonist for the treatment of hypokalemia.

Fifty patients were enrolled at 17 centers. Forty-three of the patients had Cushing's disease, 4 had ectopic ACTH tumors, and 3 had adrenal carcinoma. Patients were separated into a diabetes cohort (29 patients) and a hypertension cohort (21 patients), and efficacy was evaluated in each cohort. Treatment was initiated with mifepristone 300 mg/day, which could be increased to 600 mg after 2 weeks. Further increases by 300-mg increments were allowed every 4 weeks with a maximum dosage of 900–1200 mg/day based on weight. The mean ± SD dose at the final study visit was 732 ± 366 mg/day.

In the diabetes cohort, patients were required to have received stable antidiabetic regimens before enrollment and the regimens could not be advanced during the study. The primary end point was a reduction in the area under the curve (AUC) for glucose of at least 25% as measured with an oral glucose tolerance test. This test was chosen because it could be used for evaluation of patients with either diabetes or impaired glucose tolerance. In the hypertension cohort, the primary end point was the change in diastolic blood pressure from baseline to week 24 with response defined as a reduction of at least 5 mm Hg. Secondary end points included other clinical responses compared to baseline as evaluated by an independent data review board at weeks 6, 10, 16, and 24. This board evaluated glucose homeostasis, blood pressure, lipid levels, weight and body composition, clinical appearance, strength, and neuropsychological and quality of life scales using validated methods.

Thirty-four patients completed the study: 20 in the diabetes cohort and 14 in the hypertension cohort. Reasons for withdrawal were adverse events (7), death (2), withdrawn consent (5), and other (2). Deaths were related to progression of underlying malignancy. A modified intent-to-treat analysis was used. All patients who received at least 30 days of the study drug were included in the analysis. Of the 25 patients in the diabetes cohort who received mifepristone for at least 30 days, 60% (15 patients) responded with a 25% or greater reduction in glucose AUC during standard glucose tolerance testing ($p<0.0001$). Eighteen of the patients (72%) in the diabetes cohort had at least a 25% reduction in glucose AUC or were able to reduce antidiabetic therapy. Mean reduction in A1C was 1.1% from baseline ($p<0.001$), and 6 of 12 patients with an A1C greater than 7% at baseline had an A1C of 6% or less by the end of the trial. Mean ± SD fasting plasma glucose levels were reduced from 149 ± 74.7 mg/dl at baseline to 104.7 ± 37.5 mg/dl at 24 weeks ($p<0.03$). The doses of antidiabetic drugs were reduced in 7 of 15 patients. Of the 12 patients receiving insulin, 5 were able to reduce their insulin doses by at least 50%.[37]

In the hypertension cohort, 8 (38.1%) of 21 patients achieved at least a 5–mm Hg reduction in diastolic blood pressure compared to baseline ($p<0.05$). Two of these responders received spironolactone. When the change in blood pressure was evaluated in the hypertensive patients in both cohorts (diabetes plus hypertension cohort), 42.5% (17 of 40 patients) had a reduction in diastolic blood pressure of at least 5 mm Hg and 27.5% were able to reduce their antihypertensive drug doses. However, mean systolic and diastolic blood pressures were not significantly changed.[37]

Individuals in both groups showed improvement in clinical manifestations of Cushing's syndrome. Twenty-four patients lost at least 5% of baseline body weight, but 10 patients gained weight. Mean ± SD waist circumference decreased in women (−6.8 ± 5.8 cm, $p<0.001$) and men (−8.4 ± 5.9 cm, $p<0.001$). Mean percent total body fat declined by 3.6% ($p<0.001$). Mood, cognition, and quality of life scores improved. In the patients with Cushing's disease, magnetic resonance imaging demonstrated stability of the pituitary tumor, with the exception of one patient with an aggressive tumor.[37]

Limitations of this multicenter study include a relatively high dropout rate, lack of a placebo group, short study duration, and open-label design. In addition, response to therapy was largely based on clinical judgment; therefore, dosage increases, reductions, or interruptions were based on investigators' clinical judgment. This prevented assessment of dose response to drug.

Although these studies of mifepristone demonstrated clinical efficacy, combination therapy with mifepristone has yet to be evaluated. Based on knowledge of other pharmacologic agents, the use of mifepristone in combination with other available drugs for the treatment of Cushing's syndrome has potential. Because ketoconazole is readily available and has a mechanism of action distinct from that of mifepristone, the combination of mifepristone with ketoconazole is a logical choice and may have added benefit for the treatment of Cushing's syndrome. However, because ketoconazole is a CYP3A inhibitor, it can increase mifepristone concentrations and the dose of mifepristone should not exceed

300 mg/day if used in combination with ketoconazole. The use of mifepristone with metyrapone would likely be limited by the fact that both drugs may worsen hypokalemia.

Safety and Tolerability

Mifepristone has a black-box warning regarding its ability to cause termination of pregnancy. Premenopausal women should be tested for pregnancy before being administered this drug. Mifepristone also should be used with caution when combined with drugs metabolized by CYP3A (Table 3), in patients receiving systemic corticosteroids for a transplant or immunosuppression, in women with risk of vaginal bleeding or endometrial changes, and in patients with known prior hypersensitivity.[18] Due to its antiprogesterone effects, the drug will interfere with the effectiveness of hormonal contraception. The use of nonhormonal forms of contraception should be advised.[18]

Serious reactions include adrenal insufficiency, hypokalemia, vaginal bleeding, QT prolongation, exacerbation of conditions treated with corticosteroids, and *Pneumocystis jiroveci* infection. Adrenal insufficiency occurred in 2 of the 50 subjects during a clinical trial.[18] Although uncommon, it is important to monitor clinically for signs of adrenal insufficiency, because this cannot be measured biochemically while the patient is receiving mifepristone. If adrenal insufficiency occurs, treatment should be initiated promptly with potent high-dose glucocorticoids to overcome the glucocorticoid receptor–blocking effect of mifepristone and mifepristone should be discontinued. Because the half-life of mifepristone is long (85 hours), treatment with glucocorticoids should continue for at least 2 weeks. Mifepristone can be reintroduced cautiously at a lower dose after resolution of the adrenal insufficiency.[18]

Hypokalemia is a common adverse effect of mifepristone, occurring in 34% of patients.[37] This is thought to be a result of increased binding of cortisol to mineralocorticoid receptors. Because mifepristone blocks negative feedback by cortisol on ACTH-secreting pituitary adenomas,[29] ACTH and cortisol levels can rise with mifepristone therapy, resulting in increased access by cortisol to mineralocorticoid receptors as the capacity of 11β-HSD is exceeded.[1, 2] Because hypokalemia is a prominent feature of Cushing's syndrome even in the absence of mifepristone, it should be corrected before the initiation of mifepristone, and potassium levels should be monitored closely during treatment. Consideration can be given to the addition of a mineralocorticoid receptor antagonist such as spironolactone if hypokalemia is persistent despite potassium supplementation.[18, 36, 38] Because of the potential for activation of mineralocorticoid receptors to worsen cardiovascular disease, mifepristone should be used with caution in such patients.[38]

Adverse reactions occurring in at least 20% of patients include nausea, fatigue, headache, hypokalemia, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite, and endometrial hyperplasia.[18] Other laboratory abnormalities found were a reduction in high-density lipoprotein cholesterol levels and asymptomatic elevations in thyroid-stimulating hormone levels. Recommended monitoring should include measurement of potassium levels, clinical assessment of adrenal insufficiency, and yearly vaginal ultrasound in women.

Dosing and Administration

Mifepristone should be administered as a once-daily oral dose with food and should be taken this way consistently to avoid changes in plasma concentrations. The starting dosage is 300 mg/day, which may be escalated by 300 mg every 2–4 weeks, not to exceed a dosage of 1200 mg/day or 20 mg/kg/day. The maximum dosage for patients with renal or mild-to-moderate hepatic impairment should be 600 mg/day. If used with a CYP3A inhibitor, the maximum dose should not exceed 300 mg/day.[18] Dosing recommendations are based on the most recent multicenter trial data.[37]

Mifepristone is available as Korlym (Corcept Therapeutics Inc., Menlo Park, CA) in the United States as of May 1, 2012, through a central distribution pharmacy. The company voluntarily offered distribution through a central distribution pharmacy to ensure timely and convenient delivery of the drug to patients and to ensure that prescribers and patients are fully informed of the risks of the drug. The cost of Korlym is approximately $186 for each 300-mg pill.[39] Copayment assistance and patient assistance programs are available through the manufacturer, and further assistance is available through NORD (National Organization for Rare Disorders; 1-800-999-6673, ext. 326). Prescribers must complete a patient enrollment form and submit this to SPARK (Support Program for

Access and Reimbursement of Korlym).[40] SPARK will determine insurance eligibility and assistance.

Conclusion

Mifepristone offers an alternative mechanism of action for medical therapy of Cushing's syndrome. A recent clinical trial demonstrating improvement in hyperglycemia in patients with Cushing's syndrome led to the drug's approval by the FDA in February 2012 for use in patients with hyperglycemia secondary to Cushing's syndrome who have either failed surgery or are not surgical candidates. Unfortunately, outcomes other than reduction in glucose levels were less convincing. To our knowledge, no trials are comparing the efficacy of mifepristone with that of other available drugs for the treatment of Cushing's syndrome; therefore, choosing a medical therapy will remain largely a clinical judgment. Because mifepristone does not reduce cortisol levels, the biochemical response to the drug cannot be measured, and hypokalemia may be worsened. It also has a number of undesirable drug–drug interactions.

Because of the cost and the difficulty of monitoring clinical effectiveness, mifepristone should be administered as a second- or third-line therapy in patients with Cushing's syndrome who warrant medical management but either have failed or have a contraindication to ketoconazole or metyrapone, particularly in patients who have concomitant diabetes.

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Electronic Patent Application Fee Transmittal

Application Number:	15627359
Filing Date:	19-Jun-2017
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Filer:	Kenneth A. Weber/Jo Ann Honcik Dallara
Attorney Docket Number:	085178-1053027-011410US

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Filing Fees for Utility under 35 USC 111(a)

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Miscellaneous:				
STATUTORY OR TERMINAL DISCLAIMER	2814	1	160	160
		Total in USD ($)		**160**

Electronic Acknowledgement Receipt

EFS ID:	33798153
Application Number:	15627359
International Application Number:	
Confirmation Number:	2957
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	144579
Filer:	Kenneth A. Weber/Jo Ann Honcik Dallara
Filer Authorized By:	Kenneth A. Weber
Attorney Docket Number:	085178-1053027-011410US
Receipt Date:	21-SEP-2018
Filing Date:	19-JUN-2017
Time Stamp:	20:45:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$160
RAM confirmation Number	092418INTEFSW20472200
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PTO/AIA/25 (04-13)
Approved for use through 11/30/2020. OMB 0651-0031
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Docket Number (Optional): 085178-1053027-011410US

In re Application of: Joseph Belanoff

Application No.: 15/627,359

Filed: 06/19/2017

For: CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/82B(07-13)
Approved for use through 11/30/2014. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the above-application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
15/627,359	June 19, 2017

(Note: The boxes above maybe left blank if information is provided on form PTO/AIA/82A).

☒ I hereby appoint Practitioners associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above:

144579

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Corcept Therapeutics, Inc.

☐ Inventor or Joint Inventor (title not required below)

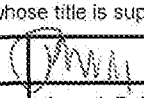
☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document)(provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (optional)	
Name	Joseph Belanoff		
Title	CEO		

NOTE: Signature – This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☒ *Total of 1 forms are submitted.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/627,359	Filing Date 06/19/2017	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $40 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $210 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	09/21/2018	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 19	Minus	** 30	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	*** 4	= 0		x $230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	Moliki I May
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	15/627,359	BELANOFF, JOSEPH K.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 9/21/18	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
Lawana Hixon

U.S. Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/627,359	06/19/2017	Joseph K. Belanoff	085178-1053027-011410US	2957

144579 7590 09/26/2018

KILPATRICK TOWNSEND & STOCKTON LLP/CORCEPT
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

EXAMINER
SIMMONS, CHRIS E

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
09/26/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipefiling@kilpatricktownsend.com
jfox@corcept.com
KTSDocketing2@kilpatrick.foundationip.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Doc Code:
TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 15/627,359

1. THE REQUEST FILED August 28, 2018 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☐ for an original nonprovisional application (Track I).
B. ☒ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;

C. filing a **request for continued examination**;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Cheryl Gibson-Baylor at (571)272-3213, Office of Petitions. In his/her absence, calls may be directed to Brian W. Brown, (571)272-5338.

Cheryl Gibson-Baylor
/Cheryl Gibson-Baylor/
[*Signature*]

Petitions Paralegal Specialist
(Title)

Office of Petitions: Decision Count Sheet | 9

Application No. 15627359

15627359

For US serial numbers: enter number only, no slashes or commas. Ex: 10123456

For PCT: enter "51+single digit of year of filing+last 5 numbers", Ex. for PCT/US05/12345, enter 51512345

Deciding Official: GIBSON-BAYLOR, C

Count (1) - Palm Credit 15627359

Decision: GRANT

FINANCE WORK NEEDED

☐ Select Check Box for YES

GRANT

Decision Type: 643 - Track One request

643

Notes:

Count (2)

Decision: n/a

FINANCE WORK NEEDED

☐ Select Check Box for YES

Decision Type: NONE

Notes:

Count (3)

Decision: n/a

FINANCE WORK NEEDED

☐ Select Check Box for YES

Decision Type: NONE

Notes:

Initials of Approving Official (if required)

Printed on: 9/24/2018

Office of Petitions Internal Document - Ver. 5.0

Office of Petitions: Routing Sheet

Application No. 15627359

This application is being forwarded to your office for further processing. A decision has been rendered on a petition filed in this application, as indicated below. For details of this decision, please see the document PET.OP.DEC filed on the same date as this document.

- [X] **GRANTED**
- [ ] **DISMISSED**
- [ ] **DENIED**

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/627,359	06/19/2017	Joseph K. Belanoff	085178-1053027-011410US

CONFIRMATION NO. 2957

POA ACCEPTANCE LETTER

144579
KILPATRICK TOWNSEND & STOCKTON LLP/CORCEPT
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

OC000000102574813

Date Mailed: 09/26/2018

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 09/21/2018.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/ldvan/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/627,359	06/19/2017	Joseph K. Belanoff	085178-1053027-011410US	2957

144579 7590 09/27/2018

KILPATRICK TOWNSEND & STOCKTON LLP/CORCEPT
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

EXAMINER	
SIMMONS, CHRIS E	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
09/27/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

KTSDocketing2@kilpatrick.foundationip.com
ipefiling@kilpatricktownsend.com
jfox@corcept.com

Applicant-Initiated Interview Summary	Application No. 15/627,359	Applicant(s) Belanoff, Joseph K.	
	Examiner CHRIS E SIMMONS	Art Unit 1629	AIA Status Yes

All participants (applicant, applicants representative, PTO personnel):

(1) CHRIS E. SIMMONS.

(3) CHARLIE ROBB.

(2) KENNETH WEBER.

(4) _____.

Date of Interview: 20 September 2018.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☑103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 1,3-4,6,12,21 and 30.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicant argues that the language in the insert reference that discuss the titration of the mifepristone cannot apply to the language in the reference where mifepristone is administered with a strong CYP3A inhibitor. Applicant points out that the insert teaches "use of strong CYP3A Inhibitors: Concomitant use can increase mifepristone plasma levels significantly. Use only when necessary and limit mifepristone dose to 300 mg." See p. 1 of insert. Applicant opined that this actually teaches away from administering more than 300 mg of mifepristone when used concomitantly with a strong CYP3A inhibitor. Applicant further discussed that unexpected results are obtained when more than 300 mg mifepristone is combined with a strong CYP3A inhibitor. Applicant also mentioned potential amendments to the claims including adding the Cyp3A 4 inhibitors to Claim 1 and canceling claims reciting 300 mg..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/CHRIS E SIMMONS/ Examiner, Art Unit 1629	/RACHAEL E BREDEFELD/ Primary Examiner, Art Unit 1611

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

Simmons, Chris E.

From: Weber, Ken <kweber@kilpatricktownsend.com>
Sent: Thursday, September 13, 2018 6:44 PM
To: Simmons, Chris E.
Subject: U.S. Application No.: 15/627,359 Agenda for interview

U.S. Application No.: 15/627,359
Filing Date: 06/19/2017
Titled: CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
Applicant: Corcept Therapeutics, Inc.
First Inventor: Joseph Belanoff
Client Ref.:
KTS Ref.: 085178-1053027-011410US
Attn: Examiner Simmons

Dear Examiner Simmons,

I will have my admin upload a communication with the agenda for our interview on the 18th tomorrow on PAIR. The text of the agenda is provided below.

In the meanwhile, I was hoping to learn if we can do this interview in person.

AGENDA FOR INTERVIEW SCHEDULED FOR SEPTEMBER 18TH AT 3 PM EST

I. Purpose of Interview: To provide a Quick overview of the 254 pages of response filed on 7/18/18, and to summarize why the claims are not obvious

i. Claim amendment and response (pages 7-28)
ii. 5 expert declarations and CVs (pages 29-122)
iii. Exhibits 2-8 (pages 124-254)

II. Recommended papers to have ready access to:

Response (See pages 7-28)
Two Rule 132 declarations of Dr. Moraitis (See pages 29-41 and 56-60)

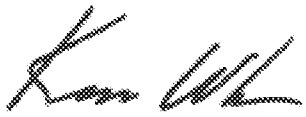
III. Substantive discussion Regarding Our Surprising Methods for Optimizing Dosing

1. Claim amendments – which, e.g., narrow the claim scope to the particular drug species of mifepristone

2. Discussion of the prior art - including the Korlym® Package Insert - which teaches away from invention of using doses above 300 mg/day, particularly in view of the declarations of Moraitis and Yau;

3. Discussion of the difference in kind as compared to prior art, and of the surprising advantages provided by the claimed invention.

Thanks,



KILPATRICK TOWNSEND
ATTORNEYS AT LAW

Kenneth A. Weber, Ph.D, J.D.
Partner
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office 415 273 4714 | fax 415 520 5145 4714 | mobile 415 828-0700
kweber@kilpatricktownsend.com | My Profile | vCard

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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NOTICE OF ALLOWANCE AND FEE(S) DUE

144579 7590 12/12/2018

KILPATRICK TOWNSEND & STOCKTON LLP/CORCEPT
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

EXAMINER
SIMMONS, CHRIS E

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 12/12/2018

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/627,359	06/19/2017	Joseph K. Belanoff	085178-1053027-011410US	2957

TITLE OF INVENTION: CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500	$0.00	$0.00	$500	03/12/2019

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

144579 7590 12/12/2018

KILPATRICK TOWNSEND & STOCKTON LLP/CORCEPT
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/627,359	06/19/2017	Joseph K. Belanoff	085178-1053027-011410US	2957

TITLE OF INVENTION: CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500	$0.00	$0.00	$500	03/12/2019

EXAMINER	ART UNIT	CLASS-SUBCLASS
SIMMONS, CHRIS E	1629	514-171000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/627,359	06/19/2017	Joseph K. Belanoff	085178-1053027-011410US	2957

144579 7590 12/12/2018

KILPATRICK TOWNSEND & STOCKTON LLP/CORCEPT
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

EXAMINER	
SIMMONS, CHRIS E	

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 12/12/2018

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 15/627,359	Applicant(s) Belanoff, Joseph K.	
	Examiner CHRIS E SIMMONS	Art Unit 1629	AIA Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 9/21/2018.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file areply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 5/30/2018.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/CHRIS E SIMMONS/ Examiner, Art Unit 1629	/JEFFREY S LUNDGREN/ Supervisory Patent Examiner, Art Unit 1629

Continuation of 3. The allowed claim(s) is/are: 1,7-10,13,16-19 and 25-27

Terminal Disclaimer

The terminal disclaimer filed on 9/11/2018 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of USSN **15/627,368** has been reviewed and is accepted. The terminal disclaimer has been recorded.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Kenneth Weber on 12/4/2018.

The application has been amended as follows:

Claims 3, 12, 21 and 28-30 are cancelled.

Claim 1 is replaced ---

A method of treating Cushing's syndrome in a patient who is taking an original once-daily dose of 1200 mg or 900 mg per day of mifepristone, comprising the steps of:

reducing the original once-daily dose to an adjusted once-daily dose of 600 mg mifepristone,

administering the adjusted once-daily dose of 600 mg mifepristone and a strong CYP3A inhibitor to the patient,

wherein said strong CYP3A inhibitor is selected from the group consisting of ketoconazole, itraconazole, nefazodone, ritonavir, nelfmavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaprevir and voriconazole.

Claim 10 is replaced ---

A method of treating symptoms associated with elevated cortisol levels in a patient who is taking an original once-daily dose of 1200 mg or 900 mg per day of mifepristone, comprising the steps of:

reducing the original once-daily dose to an adjusted once-daily dose of 600 mg mifepristone,

administering the adjusted once-daily dose of 600 mg mifepristone and a strong CYP3A inhibitor to the patient,

wherein said strong CYP3A inhibitor is selected from the group consisting of ketoconazole, itraconazole, nefazodone, ritonavir, nelfmavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaprevir and voriconazole.

Claim 13, for the term "claim 12", it has been replaced --- claim 10 ---

Claim 19 is replaced ---

A method of controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome who is taking an original once-daily dose of 1200 mg or 900 mg per day of mifepristone, comprising the steps of:

reducing the original once-daily dose to an adjusted once-daily dose of 600 mg mifepristone,

administering the adjusted once-daily dose of 600 mg mifepristone and a strong CYP3A inhibitor to the patient,

wherein said strong CYP3A inhibitor is selected from the group consisting of ketoconazole, itraconazole, nefazodone, ritonavir, nelfmavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaprevir and voriconazole.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRIS E SIMMONS whose telephone number is (571)272-9065. The examiner can normally be reached on M-F: 8-4:30p.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571)272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CHRIS E SIMMONS/
Examiner, Art Unit 1629

/JEFFREY S LUNDGREN/
Supervisory Patent Examiner, Art Unit 1629

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/627,359	Belanoff, Joseph K.
	Examiner	**Art Unit**
	CHRIS E SIMMONS	1629

CPC							
Symbol						**Type**	**Version**
A61K	/	31	/	575		F	2013-01-01
A61K	/	31	/	496		I	2013-01-01
A61K	/	45	/	06		I	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
A61K	/	31	/	567	I	1	1	2013-01-01
A61K	/	2300	/	00	A	1	2	2013-01-01
A61K	/	31	/	496	I	2	1	2013-01-01
A61K	/	2300	/	00	A	2	2	2013-01-01

/CHRIS E SIMMONS/ Examiner, Art Unit 1629	04 December 2018	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	13	
/JEFFREY S LUNDGREN/ SPE, Art Unit 1629	07 December 2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office — Part of Paper No.: 20181112

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/627,359	Belanoff, Joseph K.
	Examiner	**Art Unit**
	CHRIS E SIMMONS	1629

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	31	/	575
A61K	/	31	/	567

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

/CHRIS E SIMMONS/ Examiner, Art Unit 1629	04 December 2018	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	13	
/JEFFREY S LUNDGREN/ SPE, Art Unit 1629	07 December 2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office — Part of Paper No.: 20181112

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/627,359	Belanoff, Joseph K.
	Examiner	**Art Unit**
	CHRIS E SIMMONS	1629

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	5	10	10	19		28								
	2		11		20		29								
	3		12		21		30								
	4	6	13		22										
	5		14		23										
	6		15		24										
2	7	7	16	11	25										
3	8	8	17	12	26										
4	9	9	18	13	27										

/CHRIS E SIMMONS/ Examiner, Art Unit 1629	04 December 2018	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	13	
/JEFFREY S LUNDGREN/ SPE, Art Unit 1629	07 December 2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office

Part of Paper No.: 20181112

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/627,359	Belanoff, Joseph K.
	Examiner	Art Unit
	CHRIS E SIMMONS	1629

CPC - Searched*		
Symbol	**Date**	**Examiner**
A61K 31/575,567	12/04/2018	CS
A61K 45/06	12/04/2018	CS
A61P 3/10	12/04/2018	cs

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	**Date**	**Examiner**
EAST, Inventor search	9/17/2017	CS
Google :"mifepristone adjusting dosage";"mifepristone CYP450 3A inhibitors is necessary, the dose should be limited to 300 mg per day"	9/17/2017	CS
EAST, Inventor search		
Google "ritinovir metabolism"	05/29/2018	CS
EAST, Inventor search	11/12/2018	cs
scifinder	11/12/2018	cs
Patentability Conf: Jeffrey Lundgren (SPE AU1629); Chris Simmons (Examiner 1629)	12/04/2018	CS
EAST	12/04/2018	CS

/CHRIS E SIMMONS/ Examiner, Art Unit 1629	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/627,359	Belanoff, Joseph K.
	Examiner	Art Unit
	CHRIS E SIMMONS	1629

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
A61K	31/575,567	12/04/2018	CS
A61K	45/06	12/04/2018	CS
A61P	3/10	12/04/2018	CS

/CHRIS E SIMMONS/ Examiner, Art Unit 1629	

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/627,359	Belanoff, Joseph K.
	Examiner	Art Unit
	CHRIS E SIMMONS	1629

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original									
1	1									
	2									
	3									
	4									
	5									
	6									
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3	8									
4	9									
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	28									
	29									
	30									

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L2	21785	A61K45/06.cpc.	USPAT	AND	OFF	2018/12/04 20:13
L3	24640	1 or 2	USPAT	AND	OFF	2018/12/04 20:13
L4	24640	1 or 2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/12/04 20:13
L5	332754	A61K45/06.cpc. or A61K31/575,496.cpc.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/12/04 20:14
L6	2201	5 mifepristone	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/12/04 20:14
L7	63748	(ketoconazole, itraconazole, nefazodone, ritonavir, nelfmavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaprevir voriconazole)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2018/12/04 20:15
L8	63736	(ketoconazole, itraconazole, nefazodone, ritonavir, nelfmavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaparevir voriconazole)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2018/12/04 20:15
L9	115	paritaprevir	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2018/12/04 20:15
L10	0	paritaparevir	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2018/12/04 20:16
L11	850	7 6 7	US-PGPUB; USPAT;	AND	OFF	2018/12/04 20:17

			USOCR; FPRS; EPO; JPO; DERWENT			
L12	238	11 "600" adj (mg or milligram)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/12/04 20:19
L13	850	7 6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/12/04 20:20
L14	40	12 and "600" same (ketoconazole, itraconazole, nefazodone, ritonavir, nelfmavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaparevir voriconazole or cyp3$2)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2018/12/04 20:21
L18	15	(("CORCEPT") near3 ("THERAPEUTICS") near3 ("INC")).AANM.	USPAT	AND	OFF	2018/12/04 20:46
L19	18	(("BELANOFF") near3 ("Joseph")).INV.	USPAT	AND	OFF	2018/12/04 20:46
L20	9311	mifepristone	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/12/04 20:46
L21	25607	ketoconazole	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/12/04 20:46
L22	32	L19 or L18	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/12/04 20:46
L23	8	L22 L20 L21	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/12/04 20:46
L24	1800	a61p3/10.cpc.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/12/04 20:55
L25	3	24 20 21	US-PGPUB; USPAT; USOCR;	AND	OFF	2018/12/04 20:55

			FPRS; EPO; JPO; DERWENT			
L28	403	A61K31/567.cpc.	USPAT	AND	OFF	2018/12/04 21:41
L31	64105	28 (ketoconazole, itraconazole, nefazodone, ritonavir, nelfmavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaparevir voriconazole)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2018/12/04 21:50
L35	0	28 (ketoconazole, itraconazole, nefazodone, ritonavir, nelfmavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaparevir voriconazole)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2018/12/04 21:51

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L15	11707	A61K31/575,496.cpc.	US-PGPUB; USPAT	AND	OFF	2018/12/04 20:31
L16	65876	A61K45/06.cpc.	US-PGPUB; USPAT	AND	OFF	2018/12/04 20:31
L17	73373	(15 or 16)	US-PGPUB; USPAT	AND	OFF	2018/12/04 20:32
L26	311	a61p3/10.cpc.	US-PGPUB; USPAT	AND	OFF	2018/12/04 20:56
L27	7	a61p3/10.cpc. mifepristone	US-PGPUB; USPAT	AND	OFF	2018/12/04 20:56
L29	923	A61K31/567.cpc.	US-PGPUB; USPAT	AND	OFF	2018/12/04 21:47
L30	168	29 mifepristone	US-PGPUB; USPAT	AND	OFF	2018/12/04 21:50
L32	5826675	"28" (ketoconazole, itraconazole, nefazodone, ritonavir, nelfmavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaparevir voriconazole)	US-PGPUB; USPAT	OR	OFF	2018/12/04 21:50
L33	52093	30 (ketoconazole, itraconazole, nefazodone, ritonavir, nelfmavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaparevir voriconazole)	US-PGPUB; USPAT	OR	OFF	2018/12/04 21:50
L34	0	30 (ketoconazole, itraconazole, nefazodone, ritonavir, nelfmavir, indinavir, boceprevir,	US-PGPUB;	AND	OFF	2018/12/04 21:50

		clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaparevir voriconazole)	USPAT				

12/ 4/ 2018 9:51:57 PM
C:\ Users\ csimmons\ Documents\ EAST\ Workspaces\ 15627359.wsp

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15/627,359
	Filing Date	June 19, 2017
	First Named Inventor	Joseph K. Belanoff
	Art Unit	1629
	Examiner Name	Chris E. Simmons
	Attorney Docket Number	085178-1053027-011410US

U.S. PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code [1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	E1.	9216221	B2	Dec 22, 2015	Newell-Price	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code [1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	E2.	20100135956	A1	Jun 3, 2010	Gant et al.	
	E3.	20160067264	A1	Mar 10, 2016	Newell-Price	

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code [4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	E4.	2010052445	WO	A1	May 14, 2010	University of Sheffield		
	E5.	2016187347	WO	A1	Nov 24, 2016	Corcept Therapeutics, Inc.		

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	E6.	MORGAN et al., "Mifepristone for Management of Cushing's Syndrome", Pharmacotherapy, February 21, 2013, 33(3):319-329	
	E7	VARIS et al., "The Effect of Itraconazole on the Pharmacokinetics and Pharmacodynamics of Oral Prednisolone", European Journal of Clinical Pharmacology, April 2000, 56(1):57-60	
	E8.	PCT/US2018/020336 , "International Search Report and Written Opinion", May 15, 2018, 11 pages	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.E.S/

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15/627,359
	Filing Date	June 19, 2017
	First Named Inventor	Joseph K. Belanoff
	Art Unit	1629
	Examiner Name	Chris E. Simmons
	Attorney Docket Number	085178-1053027-011410US

EXAMINER SIGNATURE			
Examiner Signature	/CHRIS E SIMMONS/ /C.E.S/	Date Considered	11/12/2018 11/12/2018

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.E.S/

Bibliographic Data

Application No: 15/627,359

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: /CHRIS E SIMMONS/ (Examiner's Signature) (Initials)

Title: CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
06/19/2017	514	1629	085178-1053027-011410US
RULE			

APPLICANTS

Corcept Therapeutics, Inc., Menlo Park, CA,

INVENTORS

Joseph K. Belanoff Menlo Park, CA, UNITED STATES

CONTINUING DATA

This application has PRO of 62466867 03/03/2017

This application has PRO of 62465772 03/01/2017

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

06/23/2017

**** SMALL ENTITY ****

STATE OR COUNTRY

UNITED STATES

ADDRESS

KILPATRICK TOWNSEND & STOCKTON LLP/CORCEPT
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309
UNITED STATES

FILING FEE RECEIVED

$3,410

PTO/SB/47 (03-09)
Approved for use through 05/31/2015. OMB 0651-0016
U.S. Patent and Trademark Office; U. S. DEPARTMENT OF COMMERCE

"FEE ADDRESS" INDICATION FORM

Address to:
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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

- OR -

Fax to:
571-273-6500

INSTRUCTIONS: The issue fee must have been paid for application(s) listed on this form. In addition, only an address represented by a Customer Number can be established as the fee address for maintenance fee purposes (hereafter, fee address). A fee address should be established when correspondence related to maintenance fees should be mailed to a different address than the correspondence address for the application. **When to check the first box below**: If you have a Customer Number to represent the fee address. **When to check the second box below**: If you have no Customer Number representing the desired fee address, in which case a completed Request for Customer Number (PTO/SB/125) must be attached to this form. For more information on Customer Numbers, see the Manual of Patent Examining Procedure (MPEP) § 403.

For the following listed application(s), please recognize as the "Fee Address" under the provisions of 37 CFR 1.363 the address associated with:

☒ Customer Number: 00197

OR

☐ The attached Request for Customer Number (PTO/SB/125) form.

PATENT NUMBER (if known)	APPLICATION NUMBER
	15/627,359

Completed by (check one)

☐ Applicant/Inventor

☒ Attorney or Agent of record 31,677 (Reg. No.)

☐ Assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

☐ Assignee recorded at Reel ___ Frame ___

/Kenneth A. Weber/
Signature

Kenneth A. Weber
Typed or Printed Name

(415) 576-0200
Requester's telephone number

December 12, 2018
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *** Total of 1 forms are submitted.**

This collection of information is required by 37 CFR 1.363. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1. 11 and 1.14. This collection is estimated to take 5 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313- 1450. DO NOT SEND COMPLETE D FORMS TO THIS ADDRESS. **SEND TO: Mail Stop M Correspondence, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Patent Application Fee Transmittal

Application Number:	15627359
Filing Date:	19-Jun-2017
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Filer:	Kenneth A. Weber/Jo Honcik Dallara
Attorney Docket Number:	085178-1053027-011410US

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	2501	1	500	500

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**500**

Electronic Acknowledgement Receipt

EFS ID:	34566118
Application Number:	15627359
International Application Number:	
Confirmation Number:	2957
Title of Invention:	CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	144579
Filer:	Kenneth A. Weber/Jo Honcik Dallara
Filer Authorized By:	Kenneth A. Weber
Attorney Docket Number:	085178-1053027-011410US
Receipt Date:	12-DEC-2018
Filing Date:	19-JUN-2017
Time Stamp:	16:08:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$500
RAM confirmation Number	121318INTEFSW16093600
Deposit Account	201430
Authorized User	Jo Honcik Dallara

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	IssueFeeTransmittal_1053027l.pdf	95026 5c19c0237081e19dd07a1bdec4e10e392ec09721	no	1
Warnings:					
Information:					
2	Maintenance Fee Address Change	FeeAddress_1053027.pdf	149151 32f16b4630ee2c7ee9d453d93a3572684ab6981a	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30838 e813e9d5e9e6b17e72c38a706451dea4ba973267	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	275015		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

144579 7590 12/12/2018

KILPATRICK TOWNSEND & STOCKTON LLP/CORCEPT
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Suite 2800
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Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

Jo Ann Honcik Dallara	(Typed or printed name)
/Jo Ann Honcik Dallara/	(Signature)
December 12, 2018	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/627,359	06/19/2017	Joseph K. Belanoff	085178-1053027-011410US	2957

TITLE OF INVENTION: CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500	$0.00	$0.00	$500	03/12/2019

EXAMINER	ART UNIT	CLASS-SUBCLASS
SIMMONS, CHRIS E	1629	514-171000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☒ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 KILPATRICK TOWNSEND & STOCKTON LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Corcept Therapeutics, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Menlo Park, California

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 20-1430

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Kenneth A. Weber/ Date December 12, 2018

Typed or printed name Kenneth A. Weber Registration No. 31,677

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/627,359	02/05/2019	10195214	085178-1053027-011410US	2957

144579 7590 01/16/2019

KILPATRICK TOWNSEND & STOCKTON LLP/CORCEPT
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Joseph K. Belanoff, Menlo Park, CA;
Corcept Therapeutics, Inc., Menlo Park, CA;