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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 December 2005 (15.12.2005)

PCT

(10) International Publication Number
WO 2005/117861 A1

(51) International Patent Classification[7]: A61K 31/40, 31/00, 31/155, A61P 3/10

(21) International Application Number: PCT/EP2005/006003

(22) International Filing Date: 3 June 2005 (03.06.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/577,010 4 June 2004 (04.06.2004) US
60/604,273 25 August 2004 (25.08.2004) US

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF ORGANIC COMPOUNDS

(57) Abstract: A method for improving glucose control by administering metformin in combination with a DPP-lV inhibitor to a patient in need thereof, in an amount sufficient to control the glucose level over an extended period of time.

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Use of Organic compounds

The invention relates to a method of treatment and a diagnostic method, wherein the patient is treated with a Dipeptidyl peptidase IV inhibitor (DPP-IV inhibitor) or a pharmaceutically acceptable salt thereof and metformin over an extended period of time preferably one year or more.

The treated patients are preferably suffering from hyperglycemia such as diabetes mellitus preferably non-insulin-dependent diabetes mellitus or Impaired Glucose Metabolism (IGM) preferably Impaired Glucose Tolerance (IGT).

Diabetes mellitus is a relatively common disorder (estimated at about 1% prevalence in the general population) which is characterized by hyperglycemia. There are three basic types of diabetes mellitus, type I or insulin-dependent diabetes mellitus (IDDM), type II or non-insulin-dependent diabetes mellitus (NIDDM), and type A insulin resistance. Patients with either type I or type II diabetes can become insensitive to the effects of exogenous insulin ("insulin resistant") through a variety of mechanisms. Type A insulin resistance results from either mutations in the insulin receptor gene or defects in post-receptor sites of action critical for glucose metabolism. Diabetes is generally controlled through administration of exogenous insulin (especially in type I diabetics), dietary control and exercise (especially in type II diabetics) or both.

Impaired Glucose Metabolism (IGM) is defined by blood glucose levels that are above the normal range but are not high enough to meet the diagnostic criteria for type 2 diabetes mellitus. The incidence of IGM varies from country to country, but usually occurs 2-3 times more frequently than overt diabetes. Until recently, individuals with IGM were felt to be pre-diabetics, but data from several epidemiologic studies argue that subjects with IGM are heterogeneous with respect to their risk of diabetes and their risk of cardiovascular morbidity and mortality. The data suggest that subjects with IGM, in particular IGT, do not always develop diabetes, but whether they are diabetic or not, they are, nonetheless, at high risk for cardiovascular morbidity and mortality. Among subjects with IGM, about 58% have Impaired Glucose Tolerance (IGT), another 29% have Impaired Fasting Glucose (IFG), and 13% have both abnormalities (IFG/IGT). IGT is characterized by elevated postprandial (post-meal) hyperglycemia while IFG has been defined by the ADA (see Table below) on the basis of fasting glycemic values.

The categories of Normal Glucose Tolerance (NGT), IGM and type 2 diabetes mellitus were defined by the ADA (American Diabetes Association) in 1997.
The fact that IGT is an independent risk factor in non-diabetics as well as diabetics justifies it as a new indication, separate from diabetes, for prevention and treatment of cardiovascular morbidity and mortality as well as cancer. Furthermore the stage between normoglycemia and type 2 diabetes mellitus, especially the glycemic stage, is becoming of major interest and there is a strong need for a method to inhibit or delay the progression to type 2 diabetes mellitus, and also the variety of cardiovascular and microvascular conditions and diseases as well as cancer that have been associated with IGM and especially IFG and/or IGT.

Type 2 diabetes is a progressive disease, and although monotherapy may initially control blood glucose in some patients, it is associated with a high secondary failure rate. This high incidence of therapeutic failure is a major contributor to the high rate of long-term hyperglycemia-associated complications in patients with type 2 diabetes. The limitations of single-agent therapy for maintaining glycemic control may be overcome, at least in some patients, and for a limited period of time by combining multiple oral drugs to achieve reductions in blood glucose that cannot be sustained during long-term therapy with single agents. Available data support the conclusion that in most patients with type 2 diabetes, oral monotherapy will fail and treatment with multiple drugs will be required.

But, because Type 2 diabetes is a progressive disease, even patients with good initial responses to combination therapy will eventually require an increase of the dosage or further treatment with insulin because the blood glucose level is very difficult to maintain stable for a long period of time.
Although combination therapy has the potential to enhance glycemic control, it is not without limitations. Many results indicate that the risk for hypoglycemia may increase with combination therapy, and the requirement for multiple medications may also reduce patient compliance. In addition, taking multiple antihyperglycemic drugs increases the potential for pharmacokinetic interactions with other medications that the patient may be taking.

The rational use of oral combination therapy can temporarily delay the need for multiple insulin injections, facilitate temporarily the maintenance of low glucose level or low glycosylated hemoglobin (HbA1c) level and help temporarily to prevent vascular complications.

The applicant has surprisingly discovered that DPP-IV inhibitors especially LAF237 can be used in combination with Metformin to maintain low glucose level or low glycosylated

hemoglobin (HbA1c) level over an extended period of time. Furthermore the long term treatment with such a combination has significantly less inconvenient than other combinations.

Metformin, i.e. N,N-dimethylimidocarbonimide diamide, is a known compound approved by the U.S. Food & Drug Administration for the therapeutic treatment of diabetes. The compound and its preparation are disclosed, for example, in U.S. Pat. No. 3,174,901, issued May 23, 1965. It is known that metformin is effective in the treatment of type 2 diabetes, otherwise known as non-insulin-dependent diabetes mellitus (NIDDM).

In the present context the term "metformin" is also intended to comprise any salt or crystal form, especially the metformin hydrochloride salt.

The term "DPP-IV inhibitor" is intended to indicate a molecule that exhibits inhibition of the enzymatic activity of DPP-IV and functionally related enzymes, such as from 1-100% inhibition, and specially preserves the action of substrate molecules, including but not limited to glucagon-like peptide-1, gastric inhibitory polypeptide, peptide histidine methionine, substance P, neuropeptide Y, and other molecules typically containing alanine or proline residues in the second aminoterminal position. Treatment with DPP-IV inhibitors prolongs the duration of action of peptide substrates and increases levels of their intact, undegraded forms leading to a spectrum of biological activities relevant to the disclosed invention.

DPP-IV can be used in the control of glucose metabolism because its substrates include the insulinotropic hormones Glucagon like peptide-1 (GLP-1) and Gastric inhibitory peptide (GIP). GLP-1 and GIP are active only in their intact forms; removal of their two N-terminal amino acids inactivates them. In vivo administration of synthetic inhibitors of DPP-IV prevents N- terminal degradation of GLP-1 and GIP, resulting in higher plasma concentrations of these hormones, increased insulin secretion and, therefore, improved glucose tolerance. For that purpose, chemical compounds are tested for their ability to inhibit the enzyme activity of purified CD26/DPP-IV. Briefly, the activity of CD26/DPP-IV is measured in vitro by its ability to cleave the synthetic substrate Gly-Pro-p-nitroanilide (Gly-Pro-pNA). Cleavage of Gly-Pro-pNA by DPP-IV liberates the product p-nitroanilide (pNA), whose rate of appearance is directly proportional to the enzyme activity. Inhibition of the enzyme activity by specific enzyme inhibitors slows down the generation of pNA. Stronger interaction between an inhibitor and the enzyme results in a slower rate of generation of pNA. Thus, the degree of inhibition of the rate of accumulation of pNA is a direct measure of the strength of enzyme inhibition. The accumulation of pNA is measured with a

spectrophotometer. The inhibition constant, Ki, for each compound is determined by incubating fixed amounts of enzyme with several different concentrations of inhibitor and substrate.

In the present context "a DPP-IV inhibitor" is also intended to comprise active metabolites and prodrugs thereof, such as active metabolites and prodrugs of DPP-IV inhibitors. A "metabolite" is an active derivative of a DPP-IV inhibitor produced when the DPP-IV inhibitor is metabolised. A "prodrug" is a compound that is either metabolised to a DPP-IV inhibitor or is metabolised to the same metabolite(s) as a DPP-IV inhibitor. In the present context the term "a DPP-IV inhibitor" is also intended to comprise pharmaceutical salts thereof.

DPP-IV inhibitors are known in the art. In the following reference is made to representatives of DPP-IV inhibitors:

DPP-IV inhibitors are in each case generically and specifically disclosed e.g. in WO 98/19998, DE19616 486 A1, WO 00/34241, WO 95/15309, WO 01/72290, WO01/52825, WO03/002553, WO 9310127, WO 99/61431, WO 9925719, WO 9938501, WO 9946272, WO 9967278 and WO 9967279.

Preferred DPP-IV inhibitors are described in the following patent applications; WO 02053548 especially compounds 1001 to 1293 and examples 1 to 124, WO 02067918 especially compounds 1000 to 1278 and 2001 to 2159, WO 02066627 especially the described examples, WO 02/068420 especially all the compounds specifically listed in the examples I to LXIII and the described corresponding analogues, even preferred compounds are 2(28), 2(88), 2(119), 2(136) described in the table reporting IC50, WO 02083128 such as in the claims 1 to 5 especially compounds described in examples 1 to 13 and the claims 6 to 10, US 2003096846 especially the specifically described compounds, WO 2004/037181 especially examples 1 to 33, WO 0168603 especially compounds of examples 1 to 109, EP1258480 especially compounds of examples 1 to 60, WO 0181337 especially examples 1 to 118, WO 02083109 especially examples 1A to 1D, WO 030003250 especially compounds of examples 1 to 166, most preferably 1 to 8, WO 03035067 especially the compounds described in the examples, WO 03/035057 especially the compounds described in the examples, US2003216450 especially examples 1 to 450, WO 99/46272 especially compounds of claims 12, 14, 15 and 17, WO 0197808 especially compounds of claim 2, WO 03002553 especially compounds of examples 1 to 33, WO 01/34594 especially the compounds described in the examples 1 to 4, WO 02051836 especially examples 1 to 712, EP1245568 especially examples 1 to 7, EP1258476 especially examples 1 to 32, US

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