FIG. 1

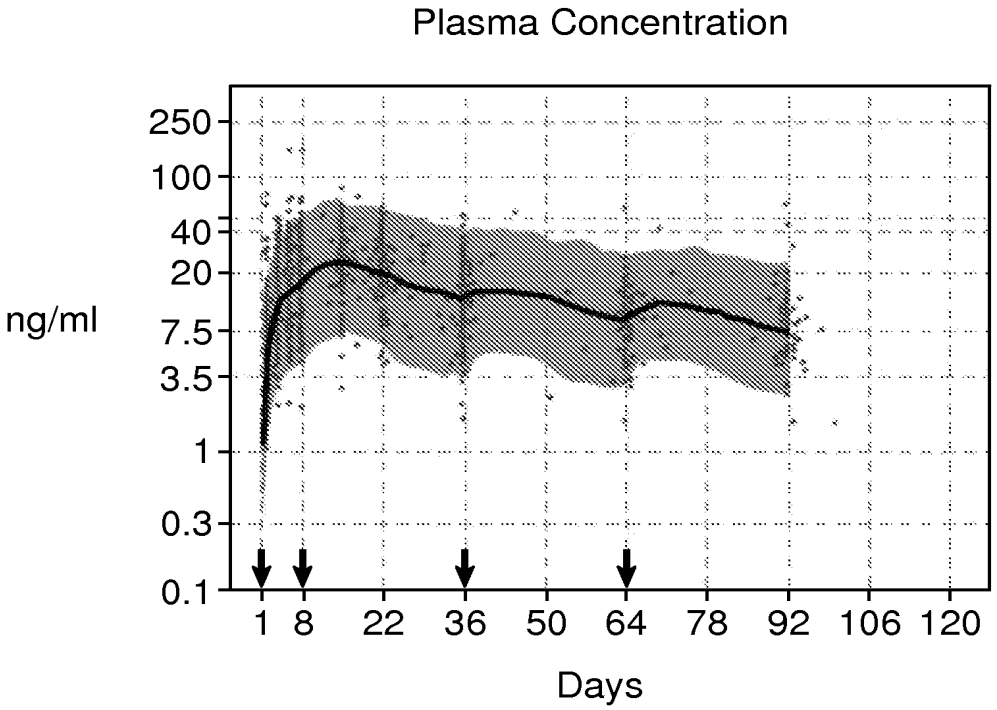
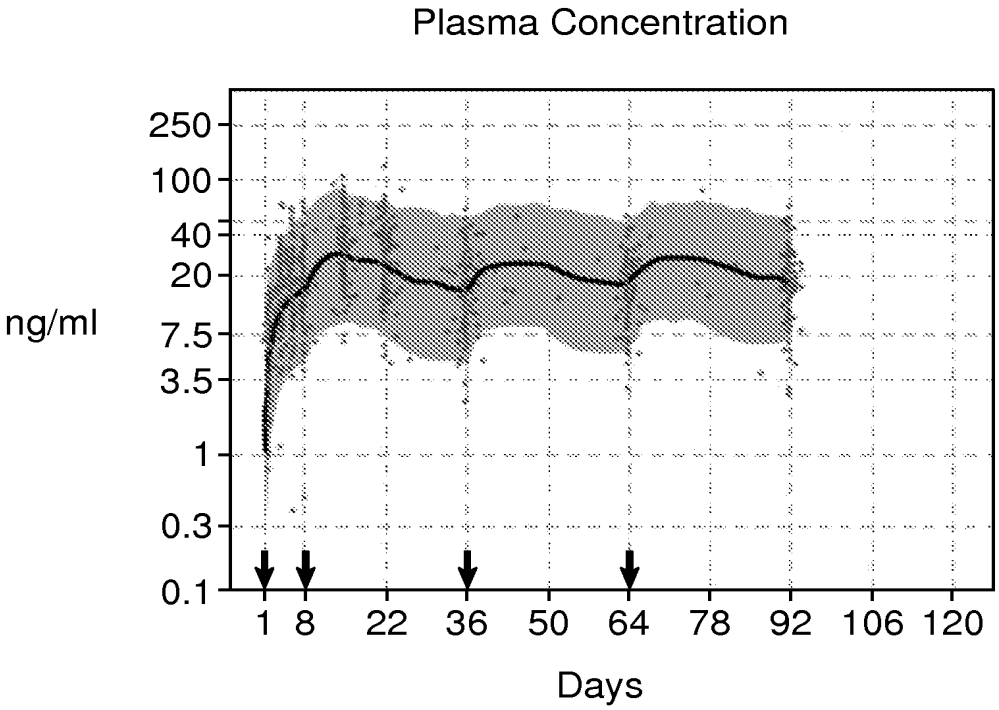

Plasma Concentration
ng/ml
250
100
40
20
7.5
3.5
1
0.3
0.1
1
8
22
36
50
64
78
92
106
120
Days

FIG. 2


Plasma Concentration
ng/ml
250
100
40
20
7.5
3.5
1
0.3
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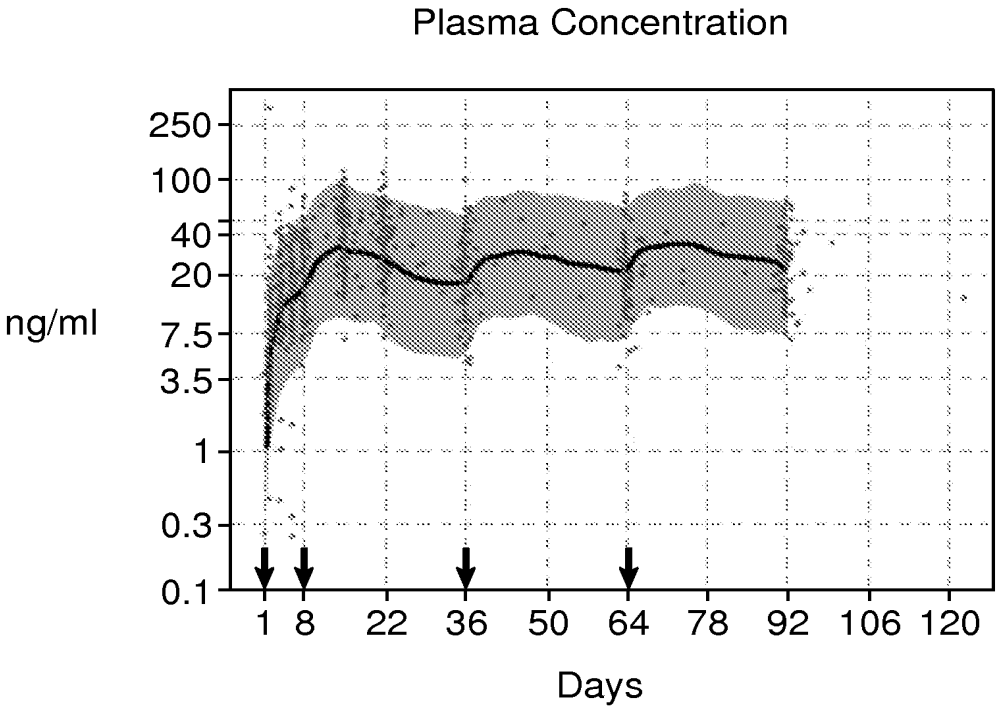
1
8
22
36
50
64
78
92
106
120
Days

FIG. 3


Plasma Concentration
ng/ml
250
100
40
20
7.5
3.5
1
0.3
0.1
1
8
22
36
50
64
78
92
106
120
Days

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DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing **OR** ☒ Declaration Submitted after Initial Filing (Surcharge (37 CFR 1.16(e)) required)

Attorney Docket Number	PRD2901USNP
First Named Inventor	Vermeulen An, et al.
COMPLETE IF KNOWN	
Application Number	
Filing Date	
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, mailing address, and citizenship are as stated below next to my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE

the specification of which

☒ is attached hereto

OR

☐ was filed on (MM/DD/YYYY) as United States Application Number or PCT International Application Number and was amended on (MM/DD/YYYY) ☐

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	Certified Copy Attached? NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

DECLARATION - Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	
61/014,918 61/120,276	12/19/2007 12/05/2008	☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status

I hereby appoint:

☒ Practitioners at Customer Number **000027777** →

Place Customer Number Bar Code Label Here

AND

☐ Practitioner(s) named below:

Name Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Address all telephone calls to Hal B. Woodrow at telephone number (732) 524-2976.

Direct all correspondence to: ☒ Customer Number or Bar Code Label **000027777** OR ☐ Correspondence address below

Name:		
Address:		
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Country	**Telephone:**	**Fax:**

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NAME OF SOLE OR FIRST INVENTOR: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any]) An	**Family Name or Surname** Vermeulen
Inventor's Signature	**Date**

Residence: City Beerse	**State** BE	**Country** BE	**Citizenship** BE
Mailing Address Turnhoutseweg 30			
City Beerse	**State** BE	**ZIP**	**Country** BE

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SECOND INVENTOR: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any]) Alfons	**Family Name or Surname** Wouters
Inventor's Signature	**Date**

Residence: City Beerse	**State** BE	**Country** BE	**Citizenship** BE
Mailing Address Turnhoutseweg 30			
City Beerse	**State** BE	**ZIP**	**Country** BE

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF THIRD INVENTOR: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	**Family Name or Surname**
Inventor's Signature	**Date**

Residence: City	**State**	**Country**	**Citizenship**
Mailing Address			
City	**State**	**ZIP**	**Country**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FOURTH INVENTOR:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname
Inventor's Signature	Date

Residence: City	State	Country	Citizenship
Mailing Address			
City	State	ZIP	Country

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF FIFTH INVENTOR:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname
Inventor's Signature	Date

Residence: City	State	Country	Citizenship
Mailing Address			
City	State	ZIP	Country

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF INVENTOR:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname
Inventor's Signature	Date

Residence: City	State	Country	Citizenship
Mailing Address			
City	State	ZIP	Country

DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

FIELD OF THE INVENTION

This invention relates to a method of treating patients in need of treatment with long acting injectable paliperidone palmitate formulations.

BACKGROUND OF THE INVENTION

Antipsychotic medications are the mainstay in the treatment of schizophrenia, schizoaffective disorder, and schizophreniform disorders. Conventional antipsychotics were introduced in the mid-1950s. These typical or first generation drugs are usually effective in controlling the positive symptoms of schizophrenia, but are less effective in moderating the negative symptoms or the cognitive impairment associated with the disease. Atypical antipsychotics or second generation drugs, typified by risperidone and olanzapine, were developed in the 1990s, and are generally characterized by effectiveness against both the positive and negative symptoms associated with schizophrenia.

Paliperidone palmitate is the palmitate ester of paliperidone (9-hydroxy-risperidone), a monoaminergic antagonist that exhibits the characteristic dopamine D_2 and serotonin (5-hydroxytryptamine type 2A) antagonism of the second-generation, atypical antipsychotic drugs. Paliperidone is the major active metabolite of risperidone. Extended release (ER) osmotic controlled release oral delivery (OROS) paliperidone, as a tablet formulation, is marketed in the United States (U.S.) for the treatment of schizophrenia and maintenance of effect.

Paliperidone palmitate is being developed as a long-acting, intramuscular (i.m.), injectable aqueous nanosuspension for the treatment of schizophrenia and other diseases that are normally treated with antipsychotic mediations. Because of extreme low water solubility, paliperidone esters such as paliperidone palmitate dissolve slowly

after an i.m. injection before being hydrolyzed to paliperidone and made available in the systemic circulation.

Many patients with these mental illnesses achieve symptom stability with available oral antipsychotic medications; however, it is estimated that up to 75% have difficulty adhering to a daily oral treatment regimen, i.e. compliance problems. Problems with adherence often result in worsening of symptoms, suboptimal treatment response, frequent relapses and re-hospitalizations, and an inability to benefit from rehabilitative and psychosocial therapies.

Paliperidone palmitate injection has been developed to provide sustained plasma concentrations of paliperidone when administered once monthly, which may greatly enhance compliance with dosing. Paliperidone palmitate was formulated as an aqueous nano suspension as is described in US Patents 6,577,545 and 6,555,544. However, after the data was analyzed from the clinical trials of this formulation it was discovered that the absorption of paliperidone from these injections was far more complex than was originally anticipated. Additionally, attaining a potential therapeutic plasma level of paliperidone in patients was discovered to be dependent on the site of injection until steady state concentration is reached. Due to the challenging nature of ensuring an optimum plasma concentration-time profile for treating patients with paliperidone it is desirable to develop a dosing regimen that fulfills this goal in patients in need of treatment.

SUMMARY OF THE INVENTION

In one embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose from about 100 mg-eq. to about 150 mg-eq. of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose from about 100 mg to about 150 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in

the gluteal a maintenance dose of about 25 to about 150 mg-eq. of paliperidone as a paliperidone ester in a sustained release formulation on between about the 34th and about the 38th day of treatment.

In one embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose from about 100 mg-eq. to about 150 mg-eq. of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose from about 100 mg to about 150 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 to about 150 mg-eq. of paliperidone as a paliperidone ester in a sustained release formulation approximately monthly from the date of the second loading dose.

In another embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose from about 100 mg-eq. to about 150 mg-eq of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on between about the 34th day and the 38th day of treatment.

In another embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid muscle of the patient in need of treatment a

second loading dose from about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation approximately monthly from the date of the second loading dose.

In another embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose from about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation approximately monthly from the date of the second loading dose.

In yet another embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a renally impaired psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose of about 75mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose of about 75 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 mg-eq. to about 75 mg-eq of paliperidone as a paliperidone palmitate in a sustained release formulation on between about the 34th and about the 38th day of treatment.

In yet another embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a renally impaired psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose of about 100mg-eq of paliperidone as a paliperidone palmitate formulated

in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose of about 75 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 mg-eq. to about 75 mg-eq of paliperidone as a paliperidone palmitate in a sustained release formulation approximately monthly from the date of the second loading dose.

In a further embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of about 75 mg-eq of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of from about 25 mg-eq. to about 50 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th day and the 38th day of treatment.

In one embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose of about 150 mg-eq. of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; thereafter administering intramuscularly a second maintenance dose of from about 25 mg-eq. to about 100 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 to about 100 mg-eq. of paliperidone as a paliperidone palmitate in a sustained release formulation on between about the 34^{th} and about the 38th day of treatment.

In a further embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need

of treatment a first loading dose from about 150 mg-eq. of paliperidone as a paliperidone palmitate ester in a sustained release formulation on the first day of treatment; thereafter administering intramuscularly in the deltoid muscle of the patient in need of treatment a maintenance dose from about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th day and the 38th day of treatment.

This and other objects and advantages of the present invention may be appreciated from a review of the present applications.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the observed versus the population pharmacokinetics model simulation for plasma paliperidone concentrations for paliperidone palmitate 150 mg eq. in the deltoid on day 1, followed by 25 mg eq. in either the deltoid or gluteus on days 8, 36, and 64.

Figure 2 shows the observed versus the population pharmacokinetics model simulation for plasma paliperidone concentrations for paliperidone palmitate 150 mg eq. in the deltoid on day 1, followed by 100 mg eq. in either the deltoid or gluteus on days 8, 36, and 64.

Figure 3 shows the observed versus the population pharmacokinetics model simulation for plasma paliperidone concentrations for paliperidone palmitate 150 mg eq. in the deltoid on day 1, followed by 150 mg eq. in either the deltoid or gluteus on days 8, 36, and 64.

DETAILED DESCRIPTION

We have discovered after extensive analysis of the clinical data that paliperidone palmitate due to its dissolution rate-limited absorption exhibits flip-flop kinetics, where the apparent half-life is controlled by the absorption rate constant. Additionally the volume of injected drug product also impacts the apparent rate constant. It was also discovered that deltoid injections result in a faster rise in initial plasma concentration, facilitating a rapid attainment of potential therapeutic concentrations. Consequently, to facilitate patients' attaining a rapid therapeutic concentration of paliperidone it is preferred to provide the initial loading dose of paliperidone palmitate in the deltoids. The loading dose should be from about 100 mg-eq. to about 150 mg-eq. of paliperidone provided in the form of paliperidone palmitate. After the first or more preferably after the second loading dose injection patients will be approaching a steady state concentration of paliperidone in their plasma and may be injected in either the deltoid or the gluteal muscle thereafter. However, it is preferred that the patients receive further injections in the gluteal muscle.

In view of these discoveries the recommended dosing regimen for patients to attain a therapeutic plasma level of paliperidone is for patients to receive the first dose of paliperidone palmitate on day 1 of treatment, followed by a second dose between days 6 to 10 of treatment, then a third dose between days 34 to 38 of treatment or monthly ±7days after the second dose. More preferably the patients will be administered a first dose on day 1, a second dose on day 8 and a third dose on or about day 36 of treatment or approximately monthly ±3 days after the second dose. The first two doses will preferably be injected in the deltoid muscle. Thereafter paliperidone palmitate will be administered by injection approximately once a month (e.g. monthly ±7days or approximately once every four weeks) thereafter. To assure that a potential therapeutic plasma level of paliperidone is attained at least a first loading dose of 150 mg-eq of paliperidone as a paliperidone palmitate ester should be administered on day one of treatment. Preferably the first two doses will be loading dose of between from about 100 mg-eq. to about 150 mg-eq. of paliperidone as a paliperidone palmitate ester to assure that a potential therapeutic plasma level of paliperidone is attained by the patient. The subsequent doses thereafter will drop to a therapeutic maintenance dose of from about 25 mg-eq. to 150 mg-eq. per month (±7 days). Preferably the maintenance dose will be from about 25mg eq. to about 100 mg eq; more preferably the maintenance dose will be from about 25mg eq. to

about 75 mg eq; and most preferably the maintenance dose initially will be about 50 mg eq., or more preferably the maintenance dose initially will be about 75 mg eq. which may be administered intramuscularly into the deltoid or gluteal muscle, but more preferably will be administered in the gluteal muscle. Those of ordinary skill in the art will understand that the maintenance dose may be titrated up or down in view of the patients condition (response to the medication and renal function).

Since paliperidone is mainly eliminated through the kidneys, patients with renal impairment will have a higher total exposure to paliperidone after i.m. injections of paliperidone palmitate. For patients with renal impairment it would desirable to adjust the loading doses to account for the increased exposure levels of patients with renal impairment. For patients with mild renal impairment the loading doses should be reduced to 75 mg-eq. for the first two loading doses. The maintenance doses should range from about 25 mg-eq. to about 75 mg-eq. and more preferably with range from about 25 mg-eq. to about 50 mg-eq. The doses would be administered on day 1 of treatment, followed by a second dose between days 6 to 10 of treatment, then a third dose between days 34 to 38 of treatment. More preferably the patients will be administered a first dose on day 1, a second dose on day 8 and a third dose on day 36 of treatment. The first two doses will preferably be injected in the deltoid muscle. Thereafter paliperidone palmitate will be administered by injection approximately once a month (e.g. one a month ±7 days or once every four weeks) thereafter. For the purpose of this patent application renal function is estimated by glomerular filtration rate (GFR) usually measured by the creatinine clearance (best calculated from a 24-hour urine collection). Creatine clearance may be estimated by the Cockcroft and Gault method based on serum creatinine concentration, as described in Prediction of creatinine clearance from serum creatinine. Nephron 1976; vol 16. pages 31-41. Patients with mild renal impairment have a creatinine clearance of 50 to <80 mL/minute.

It is recommended that the second initiation dose of paliperidone palmitate be given about one week (6-10 days) after the first dose. To avoid a missed dose, patients may be given the second dose 2 days before or after the one-week time point. Similarly, the third and subsequent injections after the initiation regimen are recommended to be given monthly. To avoid a missed monthly dose, patients may be given the injection up to 7 days before or after the monthly time point.

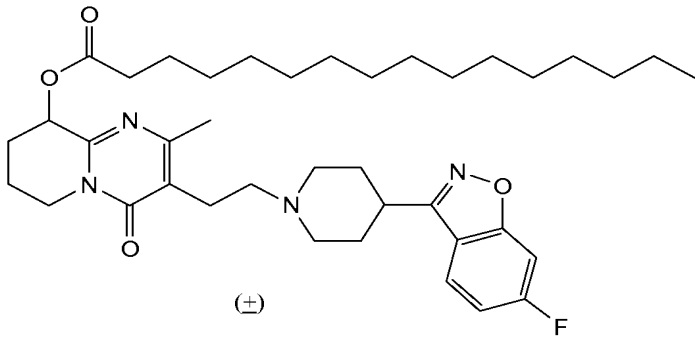
After initiation, the recommended injection cycle of paliperidone palmitate is monthly. If less than 6 weeks have elapsed since the last injection, then the previously stabilized dose should be administered as soon as possible, followed by injections at monthly intervals.

If more than 6 weeks have elapsed since the last injection, reinitiation with the same dose the patient was previously stabilized to should be resumed in the following manner: 1) a deltoid injection as soon as practically possible, followed by 2) another deltoid injection one week later, and 3) resumption of either deltoid or gluteal dosing at monthly intervals.

If more than 6 months have elapsed since the last injection, it is recommended to re-initiate dosing as described above.

Additionally, in this patient population needle length and BMI index are two related variables that need to be considered to assure patients attain therapeutic concentration of paliperidone in the desired time frame. Patients with high BMI had lower plasma concentration of paliperidone and a lessened treatment response. The lower initial plasma concentration in high BMI patients was likely due to unintended partial or complete injection into adipose tissue, instead of deep injection into muscle. However, once steady-state plasma concentration are attained BMI no longer influenced plasma concentrations or clinical efficacy. From these observations it was determined that for patients weighing <90 kg (< 200 lb) a l-inch needle will be of adequate length to use in injections to reach the muscle tissue for deltoid injections with preferably a 23 gauge needle. However, for patients with high BMIs, ≥90 kg (≥ 200 lb) a 1.5-inch needle should be used for deltoid injections. For gluteal muscle injections a 1.5-inch needle should be used. Preferably the 1.5-inch needle will be a 22-gauge needle.

Paliperidone esters are psychotic agents belonging to the chemical class of benzisoxazole derivatives, which contains a racemic mixture of (+)- and (-)-paliperidone, which are described in US Patent 5,254,556 (incorporated herein by reference). The chemical name for paliperidone palmitate is (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl hexadecanoate. The structural formula is:



(±)

Paliperidone esters may be formulated with pharmaceutical excipients into injectable dosage forms as described in US Patent 5,254,556 and US Patent 6,077,843 (incorporated herein by reference). Injectable formulations may be formulated in aqueous carriers.

Currently it is preferred to administer paliperidone palmitate in a once monthly aqueous depot. Suitable aqueous depot formulations are described in US Patent 6,077,843 (incorporated herein by reference). The aqueous formulation would preferably be a nano particle suspension of wherein the nano particles would be of an averages size of less than 2000 nm to about 100 nm. Preferably the nano particles would have an average particle size (d50) of from about 1600 nm to 400 nm and most preferably about 1400 nm to 900 nm. Preferably the d90 will be less than about 5000 nm and more preferably less than about 4400 nm. As used herein, an effective average particle size (d50) of less than 2,000 nm means that at least 50% of the particles have a diameter of less than 2,000 nm when measured by art-known conventional techniques, such as sedimentation field flow fractionation, photon correlation spectroscopy or disk centrifugation. With reference to the effective average particle size, it is preferred that at least 90%, e.g. 5,000 nm. Most preferably, 90% of the particles have a size of less than 4,400 nm.

Suitable aqueous nano particle depot formulations are described in US Patent 6,555,544 (incorporated herein by reference). In one embodiment of the present invention the formulation would comprise nanoparticles, a surfactant, a suspending agent, and optionally one or more additional ingredients selected from the group consisting of preservatives, buffers and an isotonizing agents.

Useful surface modifiers are believed to include those that physically adhere to the surface of the active agent but do not chemically bond thereto.

Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants. Representative examples of excipients include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available TWEENS™, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phtalate, noncrystalline cellulose, magnesium aluminate silicate, triethanolamine, polyvinyl alcohol (PVA), poloxamers, tyloxapol and polyvinylpyrrolidone (PVP). Most of these excipients are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986. The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two or more surface modifiers can be used in combination.

Particularly preferred surface modifiers include polyvinylpyrrolidone; tyloxapol; poloxamers, such as PLURONIC™. F68, F108 and F127 which are block copolymers of ethylene oxide and propylene oxide available from BASF; poloxamines, such as TETRONIC™ 908 (T908) which is a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine available from BASF; dextran; lecithin; Aerosol OT™ (AOT) which is a dioctyl ester of sodium sulfosuccinic acid available from Cytec Industries; DUPONOL™ P which is a sodium lauryl sulfate available from DuPont; TRITON™ X-200 which is an alkyl aryl polyether sulfonate available from Rohm and Haas; TWEEN™. 20, 40, 60 and 80 which are polyoxyethylene sorbitan fatty acid esters available from ICI Speciality Chemicals; SPAN™ 20, 40, 60 and 80 which are sorbitan esters of fatty acids;

ARLACEL™ 20, 40, 60 and 80 which are sorbitan esters of fatty acids available from Hercules, Inc.; CARBOWAX™ 3550 and 934 which are polyethylene glycols available from Union Carbide; CRODESTA™ F110 which is a mixture of sucrose stearate and sucrose distearate available from Croda Inc.; CRODESTA™ SL-40 which is available from Croda, Inc.; hexyldecyl trimethyl ammonium chloride (CTAC); bovine serum albumin and SA90HCO which is C_{18} H_{17} CH_2 $(CON(CH_3)CH_2$ $(CHOH)_4$ CH_2 $OH)_2$. The surface modifiers which have been found to be particularly useful include tyloxapol and a poloxamer, preferably, Pluronic.TM. F108 and Pluronic.TM. F68.

Pluronic.TM. F108 corresponds to poloxamer 338 and is the polyoxyethylene, polyoxypropylene block copolymer that conforms generally to the formula $HO[CH_2$ CH_2 $O]_x$ $[CH(CH_3)CH_2$ $O]_y$ $[CH_2$ CH_2 $O]_z$ H in which the average values of x, y and z are respectively 128, 54 and 128. Other commercial names of poloxamer 338 are Hodag NONIONIC™ 1108-F available from Hodag, and SYNPERONIC™ PE/F108 available from ICI Americas.

The optimal relative amount of paliperidone palmitate and the surface modifier depends on various parameters. The optimal amount of the surface modifier can depend, for example, upon the particular surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, the surface area of the antipsychotic agent, etc. The specific surface modifier preferably is present in an amount of 0.1 to 1 mg per square meter surface area of the paliperidone palmitate. It is preferred in the case of paliperidone palmitate (9-hydroxyrisperidone palmitate) to use PLURONIC™ F108 as a surface modifier, a relative amount (w/w) of both ingredients of approximately 6:1 is preferred.

The particles of this invention can be prepared by a method comprising the steps of dispersing paliperidone palmitate in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the antipsychotic agent to an effective average particle size of less than 2,000 nm. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

A general procedure for preparing the particles of this invention includes (a) obtaining paliperidone palmitate in micronized form; (b) adding the micronized paliperidone palmitate to a liquid medium to form a premix; and (c) subjecting the

premix to mechanical means in the presence of a grinding medium to reduce the effective average particle size.

The paliperidone palmitate in micronized form may be prepared using techniques known in the art. It is preferred that the particle size of the micronized paliperidone palmitate be less than about 100 μm as determined by sieve analysis. If the particle size of the micronized paliperidone palmitate is greater than about 100 μm, then it is preferred that the particles of paliperidone palmitate be reduced in size to less than 100 μm.

The micronized paliperidone palmitate can then be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of paliperidone palmitate in the liquid medium (weight by weight percentage) can vary widely and depends on the selected antipsychotic agent, the selected surface modifier and other factors. Suitable concentrations of paliperidone palmitate in compositions vary between 0.1 to 60%, preferably is from 0.5 to 30%, and more preferably, is approximately 7% (w/v). It is currently preferred to use a concentration of about 100mg eq of paliperidone per ml or about 156 mg of paliperidone palmitate per ml.

A more preferred procedure involves the addition of a surface modifier to the premix prior to its subjection to mechanical means to reduce the effective average particle size. The concentration of the surface modifier (weight by weight percentage) can vary from 0.1% to 90%, preferably from 0.5% to 80%, and more preferably is approximately 7% (w/v).

The premix can be used directly by subjecting it to mechanical means to reduce the effective average particle size in the dispersion to less than 2,000 nm. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, the antipsychotic agent and, optionally, the surface modifier, can be dispersed in the liquid medium using suitable agitation such as, for example, a roller mill or a Cowles type mixer, until a homogeneous dispersion is achieved.

The mechanical means applied to reduce the effective average particle size of the antipsychotic conveniently can take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, a planetary mill, media mills--such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the desired reduction in particle size. For media milling, the apparent viscosity of the premix preferably is anywhere between

0.1 and 1 Pa•s. For ball milling, the apparent viscosity of the premix preferably is anywhere between 1 and 100 mPa•s.

The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in form having an average size less than 3 mm and, more preferably, less than 1 mm. Such media desirably can provide the particles of the invention with shorter processing times and impart less wear to the milling equipment. The selection of the material for the grinding media is believed not to be critical. However, 95% ZrO stabilized with magnesia, zirconium silicate, and glass grinding media provide particles having levels of contamination which are acceptable for the preparation of pharmaceutical compositions. Further, other media, such as polymeric beads, stainless steel, titania, alumina and 95% ZrO stabilized with yttrium, are useful. Preferred grinding media have a density greater than 2.5 g/cm.sup.3 and include 95% ZrO stabilized with magnesia and polymeric beads.

The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For rolling mills, processing times of up to two days or longer may be required.

The particles must be reduced in size at a temperature which does not significantly degrade the antipsychotic agent. Processing temperatures of less than 30°C to 40°C are ordinarily preferred. If desired, the processing equipment may be cooled with conventional cooling equipment. The method is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process.

The surface modifier, if it was not present in the premix, must be added to the dispersion after attrition in an amount as described for the premix above. Thereafter, the dispersion can be mixed by, for example, shaking vigorously. Optionally, the dispersion can be subjected to a sonication step using, for example, a ultrasonic power supply.

Aqueous compositions according to the present invention conveniently further comprise a suspending agent and a buffer, and optionally one or more of a preservative and an isotonizing agent. Particular ingredients may function as two or more of these agents simultaneously, e.g. behave like a preservative and a buffer, or behave like a buffer and an isotonizing agent.

Suitable suspending agents for use in the aqueous suspensions according to the present invention are cellulose derivatives, e.g. methyl cellulose, sodium carboxymethyl cellulose and hydroxypropyl methyl cellulose, polyvinylpyrrolidone, alginates, chitosan, dextrans, gelatin, polyethylene glycols, polyoxyethylene- and polyoxy-propylene ethers. Preferably sodium carboxymethyl cellulose is used in a concentration of 0.5 to 2%, most preferably 1% (w/v). Suitable wetting agents for use in the aqueous suspensions according to the present invention are polyoxyethylene derivatives of sorbitan esters, e.g. polysorbate 20 and polysorbate 80, lecithin, polyoxyethylene- and polyoxypropylene ethers, sodium deoxycholate. Preferably polysorbate 20 is used in a concentration of 0.5 to 3%, more preferably 0.5 to 2%, most preferably 1.1% (w/v).

Suitable buffering agents are salt of weak acids and should be used in amount sufficient to render the dispersion neutral to very slightly basic (up to pH 8.5), preferably in the pH range of 7 to 7.5. Particularly preferred is the use of a mixture of disodium hydrogen phosphate (anhydrous) (typically about 0.9% (w/v)) and sodium dihydrogen phosphate monohydrate (typically about 0.6% (w/v)). This buffer also renders the dispersion isotonic and, in addition, less prone to flocculation of the ester suspended therein.

Preservatives are antimicrobials and anti-oxidants which can be selected from the group consisting of benzoic acid, benzyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, chlorbutol, a gallate, a hydroxybenzoate, EDTA, phenol, chlorocresol, metacresol, benzethonium chloride, myristyl-gamma-piccolinium chloride, phenylmercuric acetate and thimerosal. In particular, it is benzyl alcohol which can be used in a concentration up to 2% (w/v), preferably up to 1.5% (w/v).

Isotonizing agents are, for example, sodium chloride, dextrose, mannitol, sorbitol, lactose, sodium sulfate. The suspensions conveniently comprise from 0 to 10% (w/v) isotonizing agent. Mannitol may be used in a concentration from 0 to 7% More preferably, however, from about 1 to about 3% (w/v), especially from about 1.5 to about 2% (w/v) of one or more electrolytes are used to render the suspension isotonic, apparently because ions help to prevent flocculation of the suspended ester. In particular, electrolytes of the buffer serve as isotonizing agent.

A particularly desirable feature for an injectable depot formulation relates to the ease with which it can be administered. In particular such an injection should be

feasible using a needle as fine as possible in a span of time which is as short as possible. This can be accomplished with the aqueous suspensions of the present invention by keeping the viscosity below about 75 mPa•s, preferably below 60 mPa•s. Aqueous suspensions of such viscosity or lower can both easily be taken up in a syringe (e.g. from a vial), and injected through a fine needle (e.g a 21 G $1^1/_2$ inch, 22 G 2 inch, 22 G $1^1/_4$ inch or 23G 1 inch needle). The preferred needles for injection are 22G 22G 1 ½ inch regular wall and 23G 1 inch regular wall needles.

Ideally, aqueous suspensions according to the present invention will comprise as much prodrug as can be tolerated so as to keep the injected volume to a minimum, and as little of the other ingredients as possible. In particular, such a composition will comprise by weight based on the total volume of the composition: (a) from 3 to 20% (w/v) of the prodrug; (b) from 0.5 to 2% (w/v) of a wetting agent; (c) one or more buffering agents sufficient to render the composition neutral to very slightly basic (pH 8.5); (d) from 0.5 to 2% (w/v) of a suspending agent; (e) up to 2% (w/v) preservatives; and (f) water q.s. ad 100%. Preferably the aqueous suspension will be made under sterile conditions and no preservatives will be used. Appropriate methods to aseptically prepare paliperidone palmitate are described in WO 2006/114384 which is hereby incorporated by reference herein.

The preferred aqueous dosage form contains inactive ingredients that are polysorbate 20, polyethylene glycol 4000, citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, and water for injection. The mg of compound delivered in such a dosage form to the patient may be from 25 to about 150 mg (e.g. 25 mg, 50 mg, 75 mg, 100 mg, 150 mg,) injectable dosage form.

The term "**psychiatric patient**" as used herein, refers to a human, who has been the object of treatment, or experiment for a "mental disorder" and "mental illness" refer to those provided in the Diagnostic and Statistical Manual (DSM IV), American Psychological Association (APA). Those of ordinary skill in the art will appreciate that paliperidone esters (e.g. paliperidone palmitate), can be administered to psychiatric patients for all the known uses of risperidone. These mental disorders include, but are not limited to, schizophrenia; bipolar disorder or other disease states in which psychosis, aggressive behavior, anxiety or depression is evidenced. Schizophrenia refers to conditions characterized as schizophrenia, schizoaffective disorder and schizophreniform

disorders, in DSM-IV-TR such as category 295.xx. Bipolar Disorder refers to a condition characterized as a Bipolar Disorder, in DSM-IV-TR such as category 296.xx including Bipolar I and Bipolar Disorder II. The DSM-IV-TR was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association, and provides clear descriptions of diagnostic categories. Pathologic psychological conditions, which are psychoses or may be associated with psychotic features include, but are not limited to the following disorders that have been characterized in the DSM-IV-TR. Diagnostic and Statistical Manual of Mental Disorders, Revised, 3rd Ed. (1994). The numbers in parenthesis refer to the DSM-IV-TR categories. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for pathologic psychological conditions and that these systems evolve with medical scientific progress. Examples of pathologic psychological conditions which may be treated include, but are not limited to, Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusions (292.11), Amphetamine or

Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder

(292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

The following non-limiting examples are provided to further illustrate the present invention.

The term "**therapeutically effective amount**" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in human that is being sought by a researcher, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

Those of skill in the treatment of diseases could easily determine the effective amount of paliperidone to administer for the treatment of the diseases listed above. In general it is contemplated that an effective amount of paliperidone for the treatment of mental disorders would be from about 0.01mg/kg to about 2 mg/kg body weight. For the present invention it is preferred to dose patients with 25 mg- eq. to about 150 mg eq. paliperidone. The amount of paliperidone palmitate is provided in sufficient amount to provide the equivalent dose of paliperidone after the palmitic acid moiety is removed from the ester (e.g. 156 mg corresponds to paliperidone 100mg,). In one embodiment of present invention wherein paliperidone palmitate is administered by intramuscular injection once per month is preferred.

EXAMPLE 1

Paliperidone Palmitate Formulations

a) Crystallization in stainless steel reactor of 50L

All equipment was sterilized using dry heat sterilization.

A stainless steel reactor was charged with 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-*4H*-pyrido[1,2-a]-pyrimidin-4-one palmitate ester and ethanol parenteral grade (8 L/kg) and heated to reflux temperature (78 - 79 °C) while stirring. The product dissolved at about 70 °C. The solution was filtered at 76 °C over a sterile 0.22 μm filter into a sterile crystallization reactor. The sterile filter was then washed with heated ethanol (1 L/kg).

The filtrate was reheated to reflux and then cooled to room temperature whereupon the product crystallized. The thus obtained suspension was reheated again. The solution was cooled using differing cooling gradients (in consecutive experiments,

the mixture was reheated and cooled again; after each cooling gradient, a sample was taken and isolated using a filter. The crystals were dried in vacuo at 50 °C in Tyvek bags so as to prevent dust formation and the particle characteristics were determined.

Different batches were run, yielding product with a particle size distribution measured by laser diffraction as shown in Table 1.

Table 1

Cooling rate	Crystallization					Particle size distribution		
	Calculated cooling gradient (°C/min)	Tmax Treactor	start at … (°C) Treactor	Tjacket	start cooling (°C) Treactor	dl10 (μm)	dl50 (μm)	dl90 (μm)
1 °C/min	0.95	78	63.5	60.2	77.5	156	65	16
ASAP	3.2	75.7	61.2	17.5	75	119	36	9.2
0.5 °C/min	0.48	75.7	63.8	62.7	75	192	80	20
0.5 °C/min	0.48	75.7	63.8	62.7	75	189	81	23
0.7 °C/min	0.81	75.7	61.7	58.9	75	113	41	11
1 °C/min	0.92	75.7	62.1	54.9	75	128	52	13

b) Formulation of Composition

Table 2 provides the formulation for the F013 formulation. The F011 formulation contained the same ingredients, with the exception of citric acid and NaOH, which were not present in the F011 formulation. Since the F011 formulation does not contain NaOH or citric acid, they are not part of the aqueous phase that is added to the milled concentrate of the F011 formulation. Therefore, the concentration of buffer salts in the aqueous phase of the F011 formulation is slightly different to make the formulation isotonic.

Table 2

Name	Amount Required			
	Per ml		Quantity for 24 L	
Paliperidone palmitate (sterile grade)	156	mg	3.744	kg
Polysorbate 20 parenteral	12	mg	288	g
Citric acid monohydrate parenteral	5	mg	120	g
Disodium hydrogen phosphate anhydrous parenteral	5	mg	120	g
Sodium dihydrogen phosphate monohydrate parenteral	2.5	mg	60	g
Sodium Hydroxide all use	2.84	mg	68	g
Polyethylene Glycol 4000 parenteral	30	mg	720	g
Water for injections q.s. ad	1000	µl	24	L

Equipment

- stainless steel (SS) containers
- Grinding media (Zirconium beads) + stainless steel (SS) grinding chamber
- 0.2 µm filters
- 40 µm filter
- Filling unit
- Autoclave
- Dry heat oven

Manufacturing

Zirconium beads were cleaned and rinsed using water for injections and then depyrogenised by dry heat (120 min at 260°C). Water for injections was transferred into a SS container. Polysorbate 20 was added and dissolved by mixing. The solution was sterilized by filtration through a sterile 0.2 µm filter into a sterilized SS container. Paliperidone palmitate ester (sterile grade) as prepared in the previous examples was dispersed into the solution and mixed until homogeneous. The suspension was milled aseptically in the grinding chamber using Zirconium beads as grinding media until the required particle size was reached. The suspension was filtered aseptically through a 40 µm filter into a sterilized SS container

Water for injections was transferred into a SS container, citric acid monohydrate parenteral, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide all use, polyethylene glycol 4000 were added and mixed until dissolved. This solution was sterilized by filtration through a sterile 0.2 µm filter and transferred aseptically into the suspension. The final suspension was mixed until homogeneous. The suspension was filled aseptically into sterile syringes. The target dose volume was between 0.25 ml and 1.50 ml depending on the dose needed.

Table 3

Dose volume	Target limit	lower limit	upper limit
0.25 ml - 1.00 ml	identical to dose volume	target limit – (target limit x 0.05)	target limit x 1.05
1.25 ml - 1.50 ml	identical to dose volume	target limit – (target limit x 0.025)	target limit x 1.025

Sterilization

All aseptic manipulations and sterilization processes were carried out according to FDA and European regulatory guidelines.

Apparatus

Sterilization was done by steam sterilization ($F_0 \geq 15$) of following equipment :

- SS containers
- Zirconium beads + grinding chamber
- 0.2 µm filters
- 40 µm filter
- filling pump

Immediate container

- 1 ml long transparent plastic (COC) syringe with luer lock.
- rubber tip cap, FM257/2 dark grey
- rubber plunger stopper, 1 ml long, 4023/50, Flurotec B2-40

- 2.25ml transparent plastic (COC) syringe with luer lock.

- rubber tip cap, FM257/2 dark grey
- rubber plunger stopper, 1-3 ml, 4023/50, Flurotec B2-40
-

The empty syringes with pre-assembled tip-caps were sterilized by gamma-irradiation (dose ≥ 25 kGy). The rubber plunger stoppers were sterilized by means of steam sterilization (F_0 ≥1□.

EXAMPLE 2

Evaluation of the Pharmacokinetic Profile of Gluteal Versus Deltoid Intramuscular Injections of paliperidone palmitate 100 mg Equivalent in patients with Schizophrenia

This study was performed to characterize and compare the pharmacokinetic profile of paliperidone palmitate (formulated as described above) following four intramuscular injections in the deltoid or gluteal muscle.

Method

In this multiple-dose, open-label, parallel-group study, patients with schizophrenia were randomized to receive four consecutive intramuscular injections (days 1, 8, 36 and 64) of paliperidone palmitate 100 mg-eq. administered into either the deltoid (n=24) or gluteal muscle (n=25). Plasma samples for pharmacokinetic analyses were collected. The total paliperidone concentration was calculated as the sum of both enantiomers.

Results

The median C_{max} for paliperidone was higher in the deltoid versus the gluteal muscle after the second (31.3 versus 24.1 ng/mL) and fourth (23.7 versus 22.3 ng/mL) injections. After four injections, median AUC_{∞} was similar for both injection sites; C_{max} and AUC_{τ} for paliperidone were 30% (90% CI= 100.56% - 168.93%) and 20% (90% CI = 93.09% - 154.69%) higher in deltoid versus gluteal muscle, respectively. Median T_{max} was similar between injection sites after the second (10 day versus 10 day) and fourth injections (5 versus 6.5 days). After four injections, the median peak-

to-trough ratio was higher (2.3 versus 1.9), with a larger intersubject variability for deltoid versus gluteal injection. An increase in median predose plasma concentration between days 8, 36 and 64 for both sites suggested subjects were not completely at steady state after four injections. Relative exposure after the fourth injection was slightly lower than after the second injection in both the deltoid and gluteal muscle. Most commonly reported adverse events (combined injection sites) were orthostatic hypotension (24%), hypotension (14%), diastolic hypotension (12%) and injection site pain (14%). There were four serious adverse events (worsening of psychosis) that led to discontinuations. There were no deaths in the study. Paliperidone palmitate was well tolerated with more favorable local tolerability profile in the gluteal versus deltoid; mean injection site pain VSA score was 3.3 for gluteal versus 10.8 for deltoid muscle (day 1, 8 hours after injection.

Conclusion

Paliperidone palmitate 100 mg-eq. injections resulted in an increased AUC_{τ} higher C_{max}, greater FI, but similar T_{max} following four consecutive injections into the deltoid versus gluteal muscle. Paliperidone palmitate 100 mg-eq. was systemically and locally well tolerated in this study.

EXAMPLE 3

Assessment of the Dose Proportionality of Paliperidone Palmitate 25, 50,100, and 150 mg eq. following Administration in the Deltoid or Gluteal Muscles

This study evaluated dose proportionality of paliperidone palmitate injections when administered into either the gluteal or deltoid muscle.

Method

A single-dose, open label, parallel-group study of 201 randomized schizophrenia subjects was performed. The subjects were assigned into eight treatment groups: paliperidone palmitate 25 (n=48), 50 (n=50), 100 (n=51) or 150 (n=52) mg-eq. injected into either the deltoid or gluteal muscle. Serial plasma samples were collected

for pharmacokinetic evaluation over 126-day period. The total paliperidone concentration was calculated as the sum of both enantiomers. Dose proportionality was assessed by linear regression model, for each injection site, with log-transformed dose-normalized AUC_∞ and C_{max} as dependent variables and log-transformed dose as predictor, respectively of C_{max} and AUC_∞ ratios of the enantiomers were documented.

Results

Slopes for log-transformed dose–normalized AUC_∞ were not significantly different from zero for deltoid (slope –0.06; p=0.036) and gluteal injections (slope –0.02; p=0.760 indicating a dose-proportional increase in AUC_∞, T_{max}, was comparable between doses but slightly earlier for deltoid (13-14 days) versus gluteal injections (13-17 days). Median C_{max} was higher with deltoid (range 5.3-11.0 ng/mL) versus gluteal (range 5.1-8.7 ng/mL) injections except for the 100 mg-eq. deltoid (slope -0.22, p=0.0062) and gluteal (slope –0.31; p<0.0001) injections, indicating a less than dose-proportional increase in C_{max}. Results of C_{max} and AUC were confirmed using pairwise comparisons. Plasma concentrations of (+)-enantiomer were consistently higher than (-)-enantiomer; (+)/(-) plasma concentrations ratio was approximately 2.4 shortly after administration and decreased to ~1.7 for both injection sites, independent of dose. After a single dose of paliperidone palmitate, subjects received concomitant oral antipsychotics. Treatment-emergent AEs (TEAs) included tachycardia (10%), headache (7%), schizophrenia (6%), insomnia (5%). Only 2% of subjects discontinued due to TEAs. No deaths were reported.

Conclusion

AUC_∞ increased proportionality with increasing paliperidone palmitate doses (5-150 mg-eq.), regardless of gluteal or deltoid injection. Overall, deltoid injection was associated with a higher C_{max} (except for 100 mg-eq.) and slightly earlier T_{max} compared with gluteal injections.

EXAMPLE 4

Comparison of the PK profile in the deltoid to that in the gluteal

The plasma concentration-time profile of paliperidone after single i.m. injection of the paliperidone palmitate formulation at 25-150mg-eq. has been documented in several studies (Table 4). Details of how the comparison of injection sites study and the dose proportionality studies were performed are provided in Examples 2 and 3.

Table 4: Table of Clinical Studies Summarized

Study	Design / Treatment / PK Objective
PHASE 1 STUDIES IN SUBJECTS WITH SCHIZOPHRENIA	
R092670-INT-12 (dose-proportionality)	S.D., OL, parallel group / single i.m. injection of F011*, 25, 50, 100 or 150 mg eq. / document PK of the F011* formulation at different doses, enantiomer disposition
R092670-USA-3	M.D., OL, randomized, parallel groups / 2 i.m. injections of R092670 (F011*) 25 or 150 mg eq., gluteal or deltoid, separated by 1 week / compare the PK after deltoid and gluteal injections, explore the relationship between R092670 PK parameters and CYP P450 genotypes
R092670-PSY-1001 (comparison of injection site)	M.D., OL, randomized, parallel groups / 4 i.m. injections of R092670 (F013) 100 mg eq. in the gluteal or deltoid muscle (on Day 1, 8, 36 and 64) / compare the PK at steady state between deltoid and gluteal injection sites
R092670-PSY-1004 (dose-proportionality)	S.D., OL, randomized, parallel groups / single i.m. injection of R092670 (F013) 25, 50, 100 or 150 mg eq. in the gluteal or deltoid muscle / evaluate dose proportionality of F013 formulation over a dose range of 25 – 150 mg eq., compare the PK after deltoid and gluteal injections

S.D.: single dose; M.D.: multiple dose; OL: open-label; DB: double blind; PK: pharmacokinetic; PC: placebo-controlled; AC: active-controlled; pali ER: paliperidone extended release; pali IR: paliperidone immediate release

F011* : Sterilized by gamma-irradiation. Otherwise, sterilized by aseptic crystallization.

The total exposure (AUC_∞) of paliperidone increased proportionally with dose after single-dose injections of 25 to 150 mg eq. paliperidone palmitate in both the deltoid and gluteal muscle. The increase in C_{max} was slightly less than dose proportional for both injections sites at doses greater than 50 mg eq. The apparent half-life (reflecting the absorption rate for this type of formulations) increased with dose from 25 days (median) after the 25 mg eq. dose to 40-49 days (median) after the 100 and 150 mg eq. dose, for both injection sites. The C_{max} of paliperidone was generally higher after single-dose injection of paliperidone palmitate in the deltoid muscle compared to the gluteal muscle (geometric mean ratio ranging from 108.75% to 164.85%) whereas this was much less pronounced for AUC_∞, (geometric mean ratio

ranging from 103.00% to 117.83%). The median apparent half-life was comparable between injection sites.

EXAMPLE 5

Description of the PK profile in the gluteal after multiple administrations

Paliperidone palmitate is a long-acting i.m. injectable, intended to release over a period of 1 month. In order to attain this long injection interval, an ester of paliperidone was prepared that has a limited solubility in a physiological environment. The ester was subsequently formulated as an aqueous suspension for i.m. injection. The rate of dissolution is governed by the particle size distribution whereby it was experimentically determined that an optimal particle size range is contained within xx – yy microm (d_{50v}). In fact, the rate of dissolution (and thus the particle size distribution) fully determines the in vivo behaviour, as was nicely demonstrated in study PSY-1002. It was found that the median C_{max} increases and t_{max} shortens with decreasing particle size, which is consistent with the hypothesis that particle size is driving the release rate. The point estimates suggest that paliperidone exposure (AUC, C_{max}) after injection of paliperidone palmitate is similar between the to-be-marketed formulation F013 and formulation F011.

Table 5: Table of Clinical Studies Summarized in Module 2.7.2

Study	Design / Treatment / PK Objective
PHASE 1 STUDIES IN SUBJECTS WITH SCHIZOPHRENIA	
R092670-BEL-4 (pilot, dose-proportionality)	M.D., OL, sequential, parallel groups / 4-6 monthly i.m. injections of F004, 50 mg eq. or 100 mg eq. or 150 mg eq. / explore M.D. PK and dose-proportionality
R092670-BEL-7 (dosing regimen)	M.D., OL, parallel groups / F004 formulation: Panel I: 100 mg eq. i.m. followed by 3 monthly i.m. injections of 50 mg eq.; Panel II: 200 mg eq. i.m. followed by 3 monthly i.m. injections of 100 mg eq.; Panel III: 300 mg eq. i.m. followed by 3 monthly i.m. injections of 150 mg eq.; Panel IV: 50 mg eq. i.m. followed by 1 week later by 4 monthly i.m. injections of 50 mg eq.; Panel V: 150 mg eq. i.m. followed by 1 week later by 4 monthly i.m. injections of 150 mg eq. / explore the M.D. PK with various dosing regimens
R092670-INT-11 (compare F004 and F011)	M.D., DB, randomized, 4-group 2-way cross-over / 4 monthly i.m. injections of F004 or F011*, 2x50 and 2x150 mg eq. / compare PK of F004 and F011* formulations; compare S.D. and M.D. PK of both formulations
R092670-PSY-1002 (IVIVC)	S.D., OL, randomized, parallel groups / single i.m. injections of 1 mg paliperidone IR, followed by single i.m. injection of 50 mg eq. R092670: 1 of 4 F013 formulations with different particle sizes, or F011 formulation with medium particle size / explore IVIVC of 4 F013 formulations, compare the PK of F011 and F013 formulations
R092670-PSY-1001 (comparison of injection site)	M.D., OL, randomized, parallel groups / 4 i.m. injections of R092670 (F013) 100 mg eq. in the gluteal or deltoid muscle (on Day 1, 8, 36 and 64) / compare the PK at steady state between deltoid and gluteal injection sites

S.D.: single dose; M.D.: multiple dose; OL: open-label; DB: double blind; PK: pharmacokinetic; PC: placebo-controlled; AC: active-controlled; pali ER: paliperidone extended release; pali IR: paliperidone immediate release

F011* : Sterilized by gamma-irradiation. Otherwise, sterilized by aseptic crystallization.

Pharmacokinetic theory also implies that for a formulation with such a long apparent half-life it takes 4-5 times this half-life for steady-state to be achieved. For individual patients, this means that following the first few injections, only subtherapeutic plasma concentrations are achieved. In order to overcome this problem, a loading dose regimen was developed (BEL-7), that was subsequently used in phase 2 and 3 of drug development.The dosing regimen consisting of two initial i.m. injections separated by one week followed by subsequent doses at monthly intervals resulted in a faster attainment of apparent steady state compared with a dosing regimen of one initial injection of twice the monthly dose followed by subsequent doses at monthly intervals. Somewhat higher peak-to-through fluctuations were observed with the first dosing regimen as compared with the latter one. The dosing regimen consisting of two initial

i.m. injections separated by one week followed by subsequent doses at monthly intervals was selected for further studies and is also the recommended regimen for treatment.

EXAMPLE 6

Description of the exposure range needed for efficacy using Invega data

All antipsychotic drugs currently on the market have one feature in common: they antagonize the D_2 receptor at the level of the brain. It has been empirically derived and is currently widely excepted that 65-70% occupancy is needed for antipsychotics to show clinical efficacy (Farde et al.), i.e. improvement on the PANSS scale. A too high occupancy (80-85%) will typically increase the risk to develop EPS. In order to determine the central D_2 occupancy, PET trials in human healthy volunteers are typically performed. Two such studies have been done for paliperidone: SWE-1 and SIV-101, showing that the K_D^{app} for D_2 occupancy was ranging from 4.4 to 6.4 ng/mL. Using the 65-85% occupancy window, it can be calculated that the exposure range for efficacy without an increased risk to develop EPS as compared to placebo (<5% difference in probability) is contained in the window of 7.5-40 ng/mL.

In addition, based on the results of the phase 3 program of 6 mg paliperidone ER, in which plasma samples were collected at several time points, a plasma concentration of 7.5 ng/mL was identified as the cut-off value above which 90% of the plasma concentrations were observed. The risk to develop EPS was clearly higher for dose above 9 mg Invega. Calculating back, this roughly corresponds to an exposure level of 35-40 ng/mL at steady-state. This implies that there is ample evidence to support a target exposure efficacy range of 7.5-40 ng/mL. This should be the target exposure range for paliperidone after injection of the paliperidone palmitate formulation.

EXAMPLE 7

Optimal way of dosing

During the development of paliperidone palmitate, as the result of an extensive population PK analysis (refer to popPK report for paliperidone palmitate), several factors were found to slow down the release of paliperidone from the formulation, resulting in a slower build-up of plasma concentrations at the start of therapy and in more time required to reach steady-state. One factor was body mass index: the higher the BMI, the slower the dissolution (probably related to local physiological factors such

as diminished blood flow at the site of injection); the other one being volume administered: the higher the volume injected, the slower the dissolution (probably related to the nonlinear relationship between surface area and volume). This has resulted in a lower than expected exposure using the originally proposed loading dose regimen, and the need to come up with an improved loading dose scheme for all patients irrespective of BMI in order to avoid drop-out due to lack of efficacy at the start of therapy. The aim was to get patients as quickly as possible above the 7.5 ng/mL, certainly after 1 week for all doses considered (25 mg-eq. and above).

Simulation scenarios with the statistically significant covariates from the population PK analysis revealed the following features about the paliperidone PK after injection of paliperidone palmitate:

- Compared to deltoid injections, repeated administration in the gluteal muscle resulted in a delayed time to achieve steady-state (~ 4 wk longer), but did not influence the overall exposure (in terms of steady-state concentrations) to paliperidone.

- Deltoid injections resulted in a faster rise in initial plasma concentrations, facilitating a rapid attainment of potential therapeutic plasma concentrations. The deltoid injection site is therefore recommended as the initiation site for dosing paliperidone palmitate.

- Higher doses, associated with larger injection volumes, increased the apparent half-life of paliperidone, which in turn increased the time to achieve steady-state.

- Needle length was an important variable for the absorption kinetics from the deltoid injection-site and it is recommended to use a longer 1.5-inch needle for deltoid administration in heavy subjects (≥ 90 kg). Simulations indicated that the use of a longer needle in the deltoid muscle for the heavy individuals might be associated with an initial faster release of paliperidone into the systemic circulation, which could help overcome the slower absorption observed in heavier individuals described below.

- The body size variable BMI was another important covariate for paliperidone palmitate. A slower rise in initial concentrations was observed in the obese population, which possibly occurred due to the reduced speed of initial influx from the injection site. Initiating the first two injections in the deltoid muscle and using a longer 1.5-inch needle for deltoid injection in heavy subjects can mitigate this effect. These observations are consistent with the expectation that

in heavy subjects, administration into the adipose layer of the deltoid muscle can be avoided with the use of a longer injection needle.

Summarize what the optimized loading dose regimens would be here:

- 150 deltoid (day 1), 100 mg deltoid (day 8), then every 4 weeks maintenance (gluteal or deltoid) (PSY-3006, simulations – popPK report palmitate)
- 100 deltoid (day 1), 100 mg deltoid (day 8), then every 4 weeks maintenance (gluteal or deltoid) (simulations – popPK report palmitate, proposed for the label)
- 150 mg deltoid day 1, maintenance dose day 8 and then every 4 weeks (gluteal or deltoid) (PSY-3007)

Example 8

TITLE OF STUDY: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia

PHASE OF DEVELOPMENT: Phase 3

OBJECTIVES: The primary objectives of this study were to evaluate the efficacy and safety of 3 fixed doses of paliperidone palmitate administered intramuscularly (i.m.) after an initial dose of 150 mg equivalent (eq.) in the deltoid muscle followed by either deltoid or gluteal injections for a total of 13 weeks of treatment as compared with placebo in subjects with schizophrenia.

The secondary objectives were to:

- Assess the benefits in personal and social functioning (key secondary endpoint) associated with the use of paliperidone palmitate compared with placebo;
- Assess the global improvement in severity of illness associated with the use of paliperidone palmitate compared with placebo;

- Assess the dose-response and exposure-response relationships of paliperidone palmitate.

METHODS: This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, dose-response study of men and women, 18 years of age and older, who had a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of schizophrenia. The study included a screening period of up to 7 days and a 13-week double-blind treatment period. The screening period included a washout of disallowed psychotropic medications.

Subjects without source documentation of previous exposure to at least 2 doses of oral risperidone or paliperidone extended-release (ER), at least 1 dose of i.m. RISPERDAL® CONSTA® or paliperidone palmitate, or who were not currently receiving an antipsychotic medication were given 4 to 6 days of paliperidone ER 6 mg/day (or the option of oral risperidone 3 mg/day for subjects in Malaysia) for tolerability testing. Subjects who had source documentation of previous exposure to the above medications and were currently taking another antipsychotic regimen continued their current treatment through Day–1. At the beginning of the double-blind treatment period, subjects were randomly assigned in a 1:1:1:1 ratio to 1 of 4 treatment groups: placebo or paliperidone palmitate 25 mg eq., 100 mg eq., or 150 mg eq. Study medication was administered as 4 doses: an initial i.m. injection of 150 mg eq. of paliperidone palmitate or placebo followed by 3 fixed i.m. doses of placebo or paliperidone palmitate [25, 100, or 150 mg eq.] on Days 8, 36, and 64. The initial injection of study medication was given in the deltoid muscle. Subsequent injections were given either in the deltoid or gluteal muscle at the discretion of the investigator. Randomized subjects were to remain in the study for 28 days after the last injection on Day 64 with the end of study visit scheduled for Day 92 during the double-blind period. The entire study, including the screening period, lasted approximately 14 weeks.

Samples for pharmacokinetic (PK) evaluation were collected on Day 1, prior to the first injection and on Days 2, 4, 6, 8, 15, 22, 36, 64 and 92. Efficacy and safety were evaluated regularly throughout the study. A pharmacogenomic blood sample (10 mL) was collected from subjects who gave separate written informed consent for this part of the study. Participation in the pharmacogenomic research was optional. Approximately 105 to 115 mL of whole blood was collected during the study.

Number of Subjects (Planned and Analyzed): It was planned to include approximately 644 men and women in this study. A total of 652 eligible subjects from 72 centers in 8 countries were randomized and received at least 1 dose of double-blind study medication (safety analysis set); 636 subjects had both baseline and post baseline efficacy data (intent-to-treat analysis set).

Diagnosis and Main Criteria for Inclusion: Male or female subjects ≥18 years of age who met the DSM-IV diagnostic criteria for schizophrenia for at least 1 year before screening, had a Positive and Negative Syndrome Scale (PANSS) total score at screening of between 70 and 120, inclusive, and at baseline of between 60 and 120, inclusive, and had a body mass index (BMI) of >17.0 kg/m^2 to <40 kg/m^2 were eligible.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER was supplied as a 6-mg capsule-shaped tablet for the oral tolerability test (batch number 0617714/F40). Paliperidone palmitate was supplied as 25, 100, or 150 mg eq. injectable suspension (batch numbers 06K22/F13 and 07D23/F13). For the oral tolerability test, a 6-mg tablet of paliperidone ER (or the option of oral risperidone 3 mg/day for subjects in Malaysia) was administered daily for 4 to 6 days. On Day 1 of the double-blind treatment period, 150 mg eq. of paliperidone palmitate was injected in the deltoid muscle followed by 25, 100, or 150 mg eq. i.m. injections of paliperidone palmitate on Days 8, 36, and 64, injected into the deltoid or gluteal muscle at the investigator's discretion.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was supplied as 20% Intralipid (200 mg/mL) injectable emulsion (batch numbers 06K14/F00 and 07F12/F00). An injection was given on Days 1, 8, 36 and 64.

Duration of Treatment: The study consisted of a screening and washout phase of 7 days and a double-blind treatment period of 13 weeks, starting with the first injection in the deltoid muscle followed by a second injection 1 week later. All injections after Day 1 were given in either the deltoid or the gluteal muscle at the discretion of the investigator. Two subsequent injections were given at 4-week intervals.

CRITERIA FOR EVALUATION:

Pharmacokinetic Evaluations: A sparse blood sampling procedure was followed to study the paliperidone concentration-time profiles. Paliperidone plasma

concentration-time data were subject to population PK analysis using nonlinear mixed-effects modeling, and details are described in a separate report.

Efficacy Evaluations/Criteria: The primary endpoint was the change in the PANSS total score from baseline (i.e., the start of double-blind treatment, Day 1) to the end of the double-blind treatment period (i.e., Day 92 or the last post baseline assessment). The key secondary efficacy endpoint was the change in the Personal and Social Performance Scale (PSP) from baseline to the end of the double-blind treatment period. The other secondary efficacy endpoint was the change in the Clinical Global Impression-Severity (CGI-S) scores from baseline to the end of the double-blind treatment period. Other endpoints included the change from baseline in subject ratings of sleep quality and daytime drowsiness using a visual analogue scale (VAS), the onset of therapeutic effect, responder rate, and the change from baseline to end point in PANSS subscales and Marder factors.

Safety Evaluations: Safety was monitored by the evaluation of adverse events, extrapyramidal symptom (EPS) rating scales (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], Simpson and Angus Rating Scale [SAS]) scores, clinical laboratory test results, vital signs measurements, electrocardiograms (ECGs), and physical examination findings. In addition, the tolerability of injections was assessed; the investigators evaluated injection sites and the subjects assessed injection pain.

STATISTICAL METHODS: All randomized subjects who received at least 1 dose of double-blind study drug and had both baseline and at least one post baseline efficacy measurement (PANSS, PSP, or CGI-S) during the double-blind treatment period were included in the intent-to-treat efficacy analyses. The overall type I error rate for testing all paliperidone palmitate doses versus placebo for both the primary endpoint (change in PANSS total score at end point) and the key secondary efficacy endpoint (change in PSP total score at end point) was controlled at the 2-sided 0.05 significance level. The 2 families of hypotheses (in each family, 3 comparisons for each of the paliperidone palmitate doses versus placebo) were tested using a parallel gatekeeping procedure that adjusts for multiplicity using Dunnett's method in each family of hypotheses and using Bonferroni's inequality between different families of hypotheses. This procedure is referred to as the Dunnett-Bonferroni-based parallel gatekeeping procedure.

The change from baseline in PANSS total score at each visit and at end point was analyzed using an analysis of covariance (ANCOVA) model. The last observation carried forward (LOCF) method was used. The model included treatment and country as factors and baseline PANSS total score as a covariate. Treatment effect was based on the difference in least-squares mean change. Dunnett's test was used to adjust for multiple comparisons of the 3 paliperidone palmitate dosages versus placebo. Unadjusted 2-sided 95% confidence intervals were presented for the difference in least-squares mean change of each paliperidone palmitate dosage group compared with placebo. Treatment-by-country and treatment-by-baseline PANSS total score interactions were explored using the same ANCOVA model as the one for the analysis of the primary endpoint. If either term was statistically significant at the predefined 2-sided significance level of 0.10, further evaluations of the effect of other covariates were to be performed to assess the nature of the interaction and identify possible causes. In addition, to address the dose-response relationship and to facilitate the discussion of dosage selection, an analysis to compare the 3 active paliperidone palmitate dosages with each other was performed without adjustment for multiple comparisons.

The analysis of the key secondary endpoint, change in PSP score at end point, was conducted by means of an ANCOVA model with treatment and country as factors and the baseline score as the covariate. The Dunnett-Bonferroni-based parallel gatekeeping approach was used to adjust for multiple testing.

Between-group comparisons of CGI-S were performed by using an ANCOVA model on the ranks of change from baseline, with treatment and country as factors and the baseline score as the covariate.

Change from baseline over time (observed case) in the PANSS total score was explored using mixed effects linear models for repeated measures with time, treatment, country, and treatment-by-time as factors and baseline score as a covariate.

The number and percentage of subjects with treatment-emergent adverse events were summarized. Adverse events of potential clinical interest were summarized separately, including events related to EPS or changes in serum glucose or prolactin levels.

Changes from baseline in clinical laboratory tests, vital sign measurements, ECGs, body weight, BMI, and EPS scale scores were summarized by treatment group. Prolactin levels were summarized by sex. Subjects with potentially abnormal values or

changes in clinical laboratory tests, vital signs, orthostatic parameters, and ECG parameters were summarized based on predefined criteria. Frequency distributions were presented for the investigator's evaluation of the injection site, and descriptive statistics were presented for VAS scores corresponding to the subject's evaluation of injection pain.

RESULTS:

The majority of subjects in the paliperidone palmitate treatment groups (56% - 61%) received all 4 injections compared with 48% of the placebo-treated subjects. Completion rates were also higher for the paliperidone palmitate groups (52% - 55%) than for the placebo group (43%). More subjects were discontinued for lack of efficacy in the placebo group (27%) compared with the paliperidone palmitate groups (14% - 19%).

Demographic and Baseline Characteristics: The double-blind treatment groups were well matched with respect to demographic and baseline disease characteristics and psychiatric history. The 636 subjects who comprised the intent-to-treat analysis set were mainly male (67%), racially diverse (54% White, 30% Black, 14% Asian, 1% other races), and predominately between the ages of 26 and 50 years (75%). Most subjects had a primary diagnosis of paranoid schizophrenia (88%), and were highly symptomatic as indicated by a mean PANSS total score of 87.1 at baseline. There were notable differences between countries with respect to BMI and gender, with subjects enrolled at centers in the U.S. being more likely to be male and obese (i.e., BMI $\geq$30 kg/m^2) than those from centers in other countries.

Pharmacokinetics: A total of 488 subjects who were randomly assigned to receive paliperidone palmitate treatment had scheduled pharmacokinetic blood samples taken over the course of the study. The median paliperidone predose concentration for the 25 mg eq. treatment group was highest on Day 8, which is the result of the initial 150 mg eq. dose on Day 1. After Day 8, paliperidone concentrations decreased and seemed to reach steady state levels on Day 92 based on visual inspection. The median paliperidone predose concentration for the 100 mg eq. treatment group remained in the same range from Day 8 onwards. The median predose concentration for the 150 mg eq. treatment group seemed to increase up to the last study day, Day 92. The median paliperidone plasma concentrations on Day 8 were lower in subjects with high BMI

(≥25 to <30 kg/m² and ≥30 kg/m^2; overweight/obese) compared to subjects with low BMI (<25 kg/m²) for the 3 dose groups. After Day 8, no consistent trends were observed for the 3 paliperidone palmitate dose groups with respect to paliperidone plasma concentrations as a function of baseline BMI classification.

The mean and median paliperidone plasma concentrations on Day 64 for the 100 mg eq. treatment group were approximately 2-fold higher than those for the 25 mg eq. treatment group. Thus, the PK profile for the 25 mg eq. and 100 mg eq. dose groups appeared to be less than dose proportional, which is the result of the initial paliperidone palmitate 150 mg eq. injection on Day 1 in all active treatment groups. The mean and median paliperidone plasma concentrations on Day 64 for the 100 mg eq. dose were apparently dose proportional compared to the 150 mg eq. dose. A high inter-subject variability was observed in the paliperidone plasma concentrations on Days 1 and 2 with a %CV of 118.9% (Day 1) and 153.1% (Day 2). After Day 2, the inter-subject variability decreased and the %CV ranged from 50.4 to 83.4%.

Primary Efficacy Analysis: Adult subjects with schizophrenia achieved statistically significant improvements in the PANSS total score (primary efficacy endpoint) with all 3 doses of paliperidone palmitate compared to placebo (25 mg eq.: $p=0.034$; 100 mg eq.: $p<0.001$; 150 mg eq.: $p<0.001$) based on the intent-to-treat LOCF analysis and the Dunnett's test to control for multiplicity.

Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score - Change from Baseline to End Point-LOCF with the Dunnett-Bonferroni-Based Parallel Gatekeeping Procedure

(Study R092670-PSY-3007: Intent-to-Treat Analysis Set)

	Placebo (N=160)	R092670 25 mg eq. (N=155)	R092670 100 mg eq. (N=161)	R092670 150 mg eq. (N=160)
Baseline Mean (SD)	86.8 (10.31)	86.9 (11.99)	86.2 (10.77)	88.4 (11.70)
End point Mean (SD)	83.9 (21.44)	78.8 (19.88)	74.6 (18.06)	75.2 (18.59)
Change from Baseline				
Mean (SD)	-2.9 (19.26)	-8.0 (19.90)	-11.6 (17.63)	-13.2 (18.48)
P-value (minus Placebo)[a]		0.034	<0.001	<0.001
Diff. of LS Means (SE)		-5.1 (2.01)	-8.7 (2.00)	-9.8 (2.00)

[a] Based on analysis of covariance (ANCOVA) model with treatment (Placebo, R092670 25 mg eq., R092670 100 mg eq., R092670 150 mg eq.) and country as factors, and baseline value as a covariate. P-values were adjusted for multiplicity for comparison with placebo using Dunnett's test.

Note: Negative change in score indicates improvement.

Other Efficacy Results: There was a dose-response pattern with respect to the primary efficacy variable, with the mean decreases (improvement) in the PANSS total score at end point (LOCF).

Prespecified treatment-by-country and treatment-by-baseline PANSS total score interactions in the primary efficacy model were not statistically significant at the 0.10 level. An exploratory analysis additionally provided no statistical evidence for a BMI effect on treatment.

All 3 paliperidone palmitate dose groups showed a statistically significant improvement over placebo in the change in PANSS total score as of Day 22 and at every subsequent

time point, and as early as Day 8 in the paliperidone palmitate 25 mg eq. and 150 mg eq. groups.

The mean improvements in the PSP score from baseline to end point, the key secondary efficacy outcome measure, showed a dose response among the 3 paliperidone palmitate groups (25 mg eq.: 2.9; 100 mg eq.: 6.1; 150 mg eq.: 8.3); all were numerically higher than the mean improvement in the PSP score seen in the placebo group (1.7). Based on the intent-to-treat LOCF analysis of this key secondary efficacy variable, using the Dunnett-Bonferroni-based parallel gatekeeping procedure to adjust for multiplicity, the improvement in the paliperidone palmitate 100 and 150 mg eq. treatment groups reached statistical significance (100 mg eq.: $p=0.007$; 150 mg eq.: $p<0.001$) when compared with the placebo group.

The paliperidone palmitate 100 mg eq. and 150 mg eq. groups were statistically significantly superior to placebo in improving the CGI-S scores from baseline to end point (LOCF) (without multiplicity adjustment, 100 mg eq.: $p=0.005$; 150 mg eq.: $p<0.001$). Significantly more subjects treated with paliperidone palmitate 25 mg eq. (33.5%; $p=0.007$), 100 mg eq. (41.0%; $p<0.001$), and 150 mg eq. (40.0%, $p<0.001$) achieved responder status (30% or larger decrease on PANSS total scores) than with placebo (20.0%).

Based on the intent-to-treat LOCF analysis of the change from baseline to end point without statistical adjustment for multiplicity, the paliperidone palmitate 100 and 150 mg eq. groups were statistically significantly superior to the placebo group for all 5 PANSS Marder factors ($p\leq0.010$). The improvements in both negative symptoms and disorganized thoughts factor scores were statistically significantly greater in the paliperidone palmitate 25 mg eq. group compared with placebo ($p=0.032$).

Based on the intent-to-treat LOCF analysis using an ANCOVA model with no adjustment for multiplicity, the mean improvement in sleep quality in the paliperidone palmitate 100 mg eq. and 150 mg eq. groups were statistically significant ($p<0.001$ and $p=0.026$, respectively) when compared with placebo. The mean changes in daytime drowsiness in the paliperidone palmitate treatment groups were not statistically significantly different from that in the placebo group (25 mg eq.: $p=0.541$; 100 mg eq.: $p=0.340$; 150 mg eq.: $p=0.261$).

Safety Results: Paliperidone palmitate, injected at a dose of 150 mg eq. into the deltoid muscle followed by 3 i.m. injections at fixed doses of 25 mg eq., 100 mg eq., or 150 mg eq. on Days 8, 36, and 64, was generally well tolerated by adult subjects with schizophrenia during this 13-week study. Overall, the safety and tolerability results were consistent with previous clinical studies involving paliperidone palmitate, and no new safety signals were detected.

The overall summary of treatment-emergent adverse events is given below.

Overall Summary of Treatment-Emergent Adverse Events

(Study R092670-PSY-3007: Safety Analysis Set)

	Placebo (N=164) n (%)	R092670 25 mg eq. (N=160) n (%)	R092670 100 mg eq. (N=165) n (%)	R092670 150 mg eq. (N=163) n (%)	Total (N=652) n (%)
TEAE	107 (65.2)	101 (63.1)	99 (60.0)	103 (63.2)	410 (62.9)
Possibly related TEAE[a]	47 (28.7)	45 (28.1)	49 (29.7)	51 (31.3)	192 (29.4)
TEAE leading to death	0	0	0	1 (0.6)	1 (0.2)
1 or more serious TEAE	23 (14.0)	15 (9.4)	22 (13.3)	13 (8.0)	73 (11.2)
TEAE leading to permanent stop	11 (6.7)	10 (6.3)	10 (6.1)	13 (8.0)	44 (6.7)

[a] Study drug relationships of possible, probable, and very likely are included in this category.

Adverse events are coded using MedDRA version 10.1

There was 1 death in a subject in the paliperidone palmitate 150 mg eq. group after withdrawal from the study due to an adverse event (cerebrovascular accident) that began during the study. This subject received 2 injections of study medication, with the last injection administered approximately 2 weeks before the subject died. While this event was assessed as doubtfully related to study treatment by the investigator, an unblinded review by the sponsor assessed this event to be possibly related to study treatment.

The number of subjects who experienced treatment-emergent serious adverse events was higher in the placebo group than in any of the paliperidone palmitate groups (see

table above). Most serious adverse events in all treatment groups were psychiatric disorders (e.g., schizophrenia, psychotic disorder) that were likely the result of the natural course of the underlying schizophrenia. Adverse events leading to study discontinuation occurred at a similar low incidence across treatment groups.

Common treatment-emergent adverse events (≥2% of subjects in any treatment group) that occurred more frequently in the total paliperidone palmitate group (all 3 active dose groups combined) than in the placebo-treated subjects (i.e., ≥1% difference between the combined paliperidone palmitate group and the placebo group) were: injection site pain, dizziness, sedation, pain in extremity, and myalgia. An examination of treatment-emergent adverse events of potential clinical importance revealed no reports of seizure or convulsion, tardive dyskinesia, dermatologic events, neuroleptic malignant syndrome, hyperthermia, anaphylactic reaction, rhabdomyolysis, syndrome of inappropriate secretion of antidiuretic hormone, ventricular tachycardia, ventricular fibrillation, or torsades de pointes.

In general, the type and incidence of treatment-emergent adverse events did not differ as a function of baseline BMI categories (normal: <25 kg/m^2; overweight: ≥25 to <30 kg/m^2; obese: ≥30 kg/m^2).

The incidence of treatment-emergent EPS-related adverse events was low and comparable to placebo. Akathisia was the most frequently reported EPS-related adverse event (4.9% for the placebo group and 1.3%, 4.8%, 5.5% for the paliperidone palmitate 25, 100, and 150 mg eq. groups, respectively). None of the EPS-related adverse events reported in subjects receiving paliperidone palmitate were serious or treatment limiting, and only 1 was severe (musculoskeletal stiffness). Results of EPS rating scales and use of anti-EPS medication were consistent in indicating that paliperidone palmitate was associated with a low incidence of EPS.

No clinically relevant mean changes from baseline to end point in supine or standing pulse rates were apparent for any of the paliperidone palmitate doses. A similar, low percentage of subjects had pulse rate of ≥100 bpm with an increase of ≥15 bpm in the placebo and paliperidone palmitate groups (6% to 11% for standing measurements; 2% to 5% for supine measurements).

Assessment of ECG data did not demonstrate evidence of clinically significant QTc prolongation with paliperidone palmitate at doses up to 150 mg eq. No subject had a

maximum QTcLD value >480 ms or a maximal change in QTcLD >60 ms during the study.

The increases in body weight with paliperidone palmitate over the 13-week double-blind treatment period were modest in a dose-related manner, averaging 0.4, 0.7, and 1.4 kg for the 25 mg eq., 100 mg eq., and 150 mg eq. groups, respectively (-0.2 kg for placebo); corresponding mean changes in BMI from baseline to end point were 0.1, 0.3, and 0.5 kg/m^2, respectively (-0.1 kg/m^2 for placebo). A clinically relevant weight increase of at least 7% relative to baseline was seen in 13% of subjects receiving the highest dose of paliperidone palmitate (compared with 5% for placebo).

Consistent with the known pharmacology of paliperidone, increases in prolactin levels were observed with greater frequency in subjects who received paliperidone palmitate, with the largest increase seen in the 150 mg eq. group. Overall, there was a low incidence of potentially prolactin-related adverse events, despite the known propensity of paliperidone palmitate to increase serum prolactin levels. This suggests that the clinical importance of this increase in serum prolactin levels is of questionable clinical significance.

Based on mean changes from baseline to end point and the occurrence of treatment-emergent markedly abnormal laboratory test values and adverse events related to abnormal laboratory analyte findings, except for prolactin, the effects of paliperidone palmitate on the results of chemistry and hematology laboratory tests (including liver and renal function tests, serum lipid levels, and glucose levels) did not show clinically relevant differences from those of placebo.

Local injection site tolerability was good. Occurrences of induration, redness, or swelling as assessed by blinded study personnel were infrequent, generally mild, decreasing over time, and similar in incidence for the paliperidone palmitate and placebo groups. Investigator ratings of injection pain were similar for the placebo and paliperidone palmitate groups.

STUDY LIMITATIONS: This study investigated the efficacy and safety of paliperidone palmitate for acute treatment of schizophrenia over 13 weeks and does not provide information on longer term treatment. The study was not designed to detect differences between doses of paliperidone palmitate; thus, dose-related trends in efficacy and safety can only be described descriptively. The study was also not designed to demonstrate efficacy for specific subgroups of subjects, such as those from

a particular country. An independent, centralized blinded rating service was used for performing all ratings of PANSS, PSP and CGI-S for all subjects enrolled at U.S. sites. The investigators at these sites did not complete any of the ratings, which would have provided a reference for ratings provided by the rating service. Thus, data from this study cannot be used to fully evaluate the utility of using blinded independent raters for detecting treatment differences.

CONCLUSION: All 3 doses of paliperidone palmitate tested in this study - 25, 100, and 150 mg eq. - were efficacious in adult subjects with schizophrenia who were experiencing acutely exacerbated schizophrenia. Specifically, the results of the primary efficacy endpoint (change from baseline to end point in PANSS total score) demonstrated statistical superiority of paliperidone palmitate 25 mg eq., 100 mg eq., and 150 mg eq. over placebo. Significantly greater improvement in subjects' personal and social functioning (as measured by the PSP score) was also seen for the paliperidone palmitate 100 mg eq. and 150 mg eq. doses compared with placebo, and global improvement was validated by a favorable and statistically significant CGI-S change for these 2 dose groups. There was a dose response in the primary and secondary efficacy endpoints (PANSS, PSP, and CGI-S). All 3 doses of paliperidone palmitate, including the highest dose of 150 mg eq., were well tolerated, suggesting a positive benefit-risk ratio across the dose range currently studied. No new safety signal was detected.

Figures

Figures 1-3 graphically presents the observed versus population pharmacokinetics model simulation for plasma paliperidone concentrations. The line indicates the median values calculated from population pharmacokinetic simulation. The shading indicates 90% prediction interval representing the between and within subject, variability obtained using the population pharmacokinetic simulation. The circles indicate observed plasma paliperidone concentrations. The arrows indicate the days when paliperidone palmitate injection was given. As is apparent from the Figures the plasma profiles provided by initiating paliperidone with 150 mg eq. followed by a subsequent dose of 100 or 150 for days 1-36 provide a rapid rise to a therapeutic dose levels. Most preferably the dosing of paliperidone to patients should be maintained within ±25%, preferably 20% of the median plasma concentrations provided in these figures for days 1-36. For patients whose dosing continues at 100 mg eq. the preferably

the dosing of paliperidone to patients should be maintained within ±25%, preferably 20% of the median plasma concentrations provided in Figures 2 for days 1-64. For patients whose dosing continues at 150 mg eq. the preferably the dosing of paliperidone to patients should be maintained within ±25%, preferably 20% of the median plasma concentrations provided in Figures 3 for days 1-64.

WE CLAIM:

1. A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

(1) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of from about 100mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(2) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6^{th} to about 10th day of treatment; and

(3) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

2. The method of claim 1 wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30^{th} day of treatment.

3. The method of claim 1 wherein the sustained release formulation is an aqueous nanoparticle suspension.

4. A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of from about 100mg-eq. to about 150 mg-eq. of paliperidone as

paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.

5. The method of claim 4 wherein the sustained release formulation is an aqueous nanoparticle suspension.

6. The method of claim 4 wherein the first loading dose is 150 mgs-eq. of paliperidone as paliperidone palmitate.

7. The method of claim 4 wherein the first loading dose is 100 mg-eq. of paliperidone as paliperidone palmitate.

8. The method of claim 4 wherein the second loading dose is 150 mg-eq. of paliperidone as paliperidone palmitate.

9. The method of claim 4 wherein the second loading dose is 100 mg-eq. of paliperidone as paliperidone palmitate.

10. The method of claim 4 wherein the first loading dose and the second loading dose are 150 mg-eq. of paliperidone as paliperidone palmitate.

11. The method of claim 4 wherein the first loading dose and the second loading dose are 150 mg of paliperidone as paliperidone palmitate.

12. The method of claim 4 wherein the psychiatric patient is in need of treatment for psychosis.

13. The method of claim 4 wherein the psychiatric patient is in need of treatment for schizophrenia.

14. The method of claim 4 wherein the psychiatric patient is in need of treatment for bipolar disorder.

15. The method of claim 4 wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced

Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Halluciogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced

Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

17. A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

18. The method of claim 17 wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30th day of treatment.

19. The method of claim 17 wherein the sustained release formulation is an aqueous nanoparticle suspension.

20. A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as

paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 50 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.

21. The method of claim 20 wherein the sustained release formulation is an aqueous nanoparticle suspension.

22. The method of claim 20 wherein the psychiatric patient is in need of treatment for psychosis.

23. The method of claim 4 wherein the psychiatric patient is in need of treatment for schizophrenia.

24. The method of claim 4 wherein the psychiatric patient is in need of treatment for bipolar disorder.

25. The method of claim 4 wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type

(312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Halluciogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89),

Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar

Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

26. A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a maintenance dose of from about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6^{th} to about 10th day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

27. The method of claim 26 wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30^{th} day of treatment.

28. The method of claim 26 wherein the sustained release formulation is an aqueous nanoparticle suspension.

29. A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a maintenance dose of from about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.

30. The method of claim 29 wherein the sustained release formulation is an aqueous nanoparticle suspension.

31. The method of claim 29 wherein the psychiatric patient is in need of treatment for psychosis.

32. The method of claim 29 wherein the psychiatric patient is in need of treatment for schizophrenia.

33. The method of claim 29 wherein the psychiatric patient is in need of treatment for bipolar disorder.

34. The method of claim 29 wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders

(299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Halluciogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced

Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder

(295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

Abstract of the Invention

The present invention provides a method of treating patients in need of treatment with long acting injectable paliperidone palmitate formulations.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS
First Named Inventor/Applicant Name:	An Wermeulen
Filer:	Hal Brent Woodrow/Dawn Nudo
Attorney Docket Number:	PRD2901USNP

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	330	330
Utility Search Fee	1111	1	540	540
Utility Examination Fee	1311	1	220	220
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1090**

Electronic Acknowledgement Receipt

EFS ID:	4475490
Application Number:	12337144
International Application Number:	
Confirmation Number:	3172
Title of Invention:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS
First Named Inventor/Applicant Name:	An Wermeulen
Customer Number:	27777
Filer:	Hal Brent Woodrow/Dawn Nudo
Filer Authorized By:	Hal Brent Woodrow
Attorney Docket Number:	PRD2901USNP
Receipt Date:	17-DEC-2008
Filing Date:	
Time Stamp:	16:22:48
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1090
RAM confirmation Number	2089
Deposit Account	100750
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 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	Drawings-only black and white line drawings	PRD29011DRAWINGS.pdf	104697 477c62399a47fb3a8ecaab3635f984f65c93c267	no	3
Warnings:					
Information:					
2	Oath or Declaration filed	PRD2901USNPDeclaration.pdf	127287 91b0d18c7629a4cf7a509f56c37a0d45c2d57027	no	4
Warnings:					
Information:					
3		PRD2901USNP15Dec2008.pdf	274295 614d3b8fddb648fa86cc1bfdadd5142cda27f399	yes	60

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	45
Claims	46	59
Abstract	60	60

Warnings:					
Information:					
4	Fee Worksheet (PTO-06)	fee-info.pdf	33104 a91187a99c09b7c2a54262e89852d67da31ef8eb	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	539383	

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.

DocCode - SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 12337144 Document Date: 12/17/08

The presence of this form in the IFW record indicates that the following document type was received in paper and is scanned and stored in the SCORE database.

- Design Drawings

The original paper documents are in the physical artifact folder. The original documents are scanned using a higher quality capture process and stored in SCORE. A copy of these documents are scanned in IFW using the standard quality scanning process. Defects visible in both IFW and SCORE are indicative of defects in the original paper documents.

To access the documents in the SCORE database, refer to instructions developed by SIRA.

At the time of document entry (noted above):

- Examiners may access SCORE content via the eDAN interface.
- Other USPTO employees can bookmark the current SCORE URL (http://es/ScoreAccessWeb/).
- External customers may access SCORE content via the Public and Private PAIR interfaces.

Form Revision Date: October 12, 2006

PTO/SB/06 (12-04)

Filing Date: **12/17/08**

Approved for use through 7/31/2006. 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
12/337,144

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	330
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	540
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	220
TOTAL CLAIMS (37 CFR 1.16(i))	33 minus 20 =	13	x$26		OR	x$52	676
INDEPENDENT CLAIMS (37 CFR 1.16(h))	6 minus 3 =	* 3	x$110			x$220	660
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			195			390	
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2426

APPLICATION AS AMENDED – PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T 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.

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.

12-17-08

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
02/26/2009 AGOITOM 00000040 100750 12337144 01 FC:201 220.00 DA 02 FC:202 676.00 DA **Title of Invention:** 02/26/2009 AGOITOM 00000047 100750 12337144 01 FC:201 440.00 DA	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS
First Named Inventor/Applicant Name:	An Wermeulen
Filer:	Hal Brent Woodrow/Dawn Nudo
Attorney Docket Number:	PRD2901USNP

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	330	330
Utility Search Fee	1111	1	540	540
Utility Examination Fee	1311	1	220	220
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

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
12/337,144	12/17/2008	An Vermeulen	PRD2901USNP

CONFIRMATION NO. 3172

27777
PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

FORMALITIES LETTER

OC00000034764671

Date Mailed: 03/05/2009

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is unsigned.

The application is informal since it does not comply with the regulations for the reason(s) indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- A substitute specification in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125, is required. The substitute specification must be submitted with markings and be accompanied by a clean version (without markings) as set forth in 37 CFR 1.125(c) and a statement that the substitute specification contains no new matter (see 37 CFR 1.125(b)). The specification, claims, and/or abstract page(s) submitted is not acceptable and cannot be scanned or properly stored because:
  - The application papers (including any electronically submitted papers) are not in compliance with 37 CFR 1.52 because pages Pg. 12, 25-28 contain text that is written in unacceptable font or font size. The text must be written in nonscript type font (e.g., Arial, Times Roman, Courier, preferably a font size of 12) lettering style having capital letters that should be at least 0.3175 cm. (0.125 inch) high. A font with capital letters smaller than 0.3175 cm. (0.125 inch) high is only acceptable if the writing is clear and legible.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $**130** for a non-small entity, must be submitted with the missing items identified in this notice.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is $**130** for a non-small entity
- $**130** Surcharge.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

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Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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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	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/337,144	12/17/2008	1614	2426	PRD2901USNP	33	6

CONFIRMATION NO. 3172

27777
PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

FILING RECEIPT

OC000000034764670

Date Mailed: 03/05/2009

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

An Vermeulen, Beerse, BELGIUM;
Alfons Wouters, Beerse, BELGIUM;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/014,918 12/19/2007
and claims benefit of 61/120,276 12/05/2008

Foreign Applications

If Required, Foreign Filing License Granted: 02/26/2009

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/337,144**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No

Title

DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/337,144	12/17/2008	1614	2426	PRD2901USNP	33	6

CONFIRMATION NO. 3172

27777
PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

FILING RECEIPT

Date Mailed: 03/11/2009

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

An Vermeulen, Beerse, BELGIUM;
Alfons Wouters, Beerse, BELGIUM;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/014,918 12/19/2007
and claims benefit of 61/120,276 12/05/2008

Foreign Applications

If Required, Foreign Filing License Granted: 02/26/2009

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/337,144**

Projected Publication Date: 06/25/2009

Non-Publication Request: No

Early Publication Request: No

Title

DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

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The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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
12/337,144	12/17/2008	An Vermeulen	PRD2901USNP

CONFIRMATION NO. 3172

WITHDRAWAL NOTICE

27777
PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

Date Mailed: 03/11/2009

Letter Regarding a New Notice and/or the Status of the Application

If a new notice or Filing Receipt is enclosed, applicant may disregard the previous notice mailed on 03/05/2009. The time period for reply runs from the mail date of the new notice. Within the time period for reply, applicant is required to file a reply in compliance with the requirements set forth in the new notice to avoid abandonment of the application.

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web. https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If the reply is not filed electronically via EFS-Web, the reply must be accompanied by a copy of the new notice.

If the Office previously granted a petition to withdraw the holding of abandonment or a petition to revive under 37 CFR 1.137, the status of the application has been returned to pending status.

/jdchase/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	An Vermeulen et al.	Confirmation No. 3172	
Serial No.:	12/337,144	Group No.:	1614
Filed:	12/17/2008	Examiner:	Not Yet Assigned
For:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS		

CERTIFICATE OF EFS TRANSMISSION

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office on the date shown below via the "Electronic Filing System" in accordance with 37 C.F.R. § 1.6(a)(4).

Kristin Miele	/Kristin Miele/	April 27, 2009
Type or print name	Signature	Date

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

RESPONSE TO NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

Dear Sir:

In response to the Notice to File Missing Parts of Non Provisional Application dated March 5, 2009, submitted herewith is a *Declaration for Non-Provisional Patent Application and Power of Attorney* duly executed by the inventors in the above-referenced application. The Applicants understand that the requirement for a substitute specification has been withdrawn, because the Office has determined that the informalities noted in the March 5, 2009 communication do not exist.

Accompanying this response is the appropriate surcharge of $130.00 for submission of the Declaration pursuant to Section 1.16(f). The Commissioner is hereby authorized to charge the required fee to Deposit Account No. 10-0750/PRD2901USNP/HBW. (NOTE: all fees to be paid via EFS)

Respectfully submitted,

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
Phone: (732) 524-2976
Dated: April 27, 2009

By: /Hal Brent Woodrow/
Hal B. Woodrow, Reg. No. 32,501

Electronic Patent Application Fee Transmittal

Application Number:	12337144
Filing Date:	17-Dec-2008
Title of Invention:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS
First Named Inventor/Applicant Name:	An Vermeulen
Filer:	Hal Brent Woodrow/Kristin Miele
Attorney Docket Number:	PRD2901USNP

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Late filing fee for oath or declaration	1051	1	130	130
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**130**

Electronic Acknowledgement Receipt

EFS ID:	5220320
Application Number:	12337144
International Application Number:	
Confirmation Number:	3172
Title of Invention:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS
First Named Inventor/Applicant Name:	An Vermeulen
Customer Number:	27777
Filer:	Hal Brent Woodrow/Kristin Miele
Filer Authorized By:	Hal Brent Woodrow
Attorney Docket Number:	PRD2901USNP
Receipt Date:	27-APR-2009
Filing Date:	17-DEC-2008
Time Stamp:	09:30:21
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$130
RAM confirmation Number	7966
Deposit Account	100750
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 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	Applicant Response to Pre-Exam Formalities Notice	PRD2901USNP_Resp_MissingParts.pdf	178279 90d54f52accd093c78ecaad62c7e7d6e2a0fe3a3	no	1
Warnings:					
Information:					
2	Oath or Declaration filed	PRD2901USNP_ExecDEC.pdf	1302802 d552e6458bb99cc62de4d0bcc4c547a96a0fcffd	no	8
Warnings:					
Information:					
3	Fee Worksheet (PTO-875)	fee-info.pdf	30383 273450bc684b26d41ce7a820801703193068f356	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1511464		

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.

Please type a plus sign (+) inside this box [+]

PTO/SB/01 (10-00)
Approved for use through 10/31/2002. 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 contains a valid OMB control number.

DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing OR ☒ Declaration Submitted after Initial Filing (Surcharge (37 CFR 1.16(e)) required)

Attorney Docket Number	PRD2901USNP
First Named Inventor	Vermeulen An, et al.
COMPLETE IF KNOWN	
Application Number	12/337,144
Filing Date	12/17/2008
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, mailing address, and citizenship are as stated below next to my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

the specification of which

☐ is attached hereto

OR

☒ was filed on 12/17/2008 as United States Application Number 12/337,144 or PCT International Application Number ( ) and was amended on ( )

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	Certified Copy Attached? NO
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

DECLARATION - Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.
61/014,918 61/120,276	12/19/2007 12/05/2008	

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status

I hereby appoint:

☒ Practitioners at Customer Number **000027777** →

Place Customer Number Bar Code Label Here

AND

☐ Practitioner(s) named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Address all telephone calls to Hal B. Woodrow at telephone number (732) 524-2976.

Direct all correspondence to: ☒ Customer Number or Bar Code Label **000027777** OR ☐ Correspondence address below

Name:		
Address:		
Address:		
City:	**State:**	**ZIP**
Country	**Telephone:**	**Fax:**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FIRST INVENTOR:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle [if any]) An		Family Name or Surname Vermeulen	
Inventor's Signature		Date 11 March 2008	
Residence: City Beerse	State BE	Country BE	Citizenship BE
Mailing Address Turnhoutseweg 30			
City Beerse	State BE	ZIP	Country BE

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SECOND INVENTOR:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle [if any]) Alfons		Family Name or Surname Wouters	
Inventor's Signature		Date	
Residence: City Beerse	State BE	Country BE	Citizenship BE
Mailing Address Turnhoutseweg 30			
City Beerse	State BE	ZIP	Country BE

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF THIRD INVENTOR:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle [if any])		Family Name or Surname	
Inventor's Signature		Date	
Residence: City	State	Country	Citizenship
Mailing Address			
City	State	ZIP	Country

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FOURTH INVENTOR:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname
Inventor's Signature	Date
Residence: City / State / Country / Citizenship	
Mailing Address	
City / State / ZIP / Country	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF FIFTH INVENTOR:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname
Inventor's Signature	Date
Residence: City / State / Country / Citizenship	
Mailing Address	
City / State / ZIP / Country	

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NAME OF INVENTOR:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname
Inventor's Signature	Date
Residence: City / State / Country / Citizenship	
Mailing Address	
City / State / ZIP / Country	

Please type a plus sign (+) inside this box [+]

PTO/SB/01 (10-00)
Approved for use through 10/31/2002. 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 contains a valid OMB control number.

DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing OR ☒ Declaration Submitted after Initial Filing (Surcharge (37 CFR 1.16(e)) required)

Attorney Docket Number	PRD2901USNP
First Named Inventor	Vermeulen An, et al.
COMPLETE IF KNOWN	
Application Number	12/337,144
Filing Date	12/17/2008
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, mailing address, and citizenship are as stated below next to my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

the specification of which

☐ is attached hereto

OR

☒ was filed on 12/17/2008 as United States Application Number 12/337,144 or PCT International Application Number ( ) and was amended on ( ).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	Certified Copy Attached? NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

DECLARATION - Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.
61/014,918 61/120,276	12/19/2007 12/05/2008	

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status

I hereby appoint:

☒ Practitioners at Customer Number 000027777 –

AND

☐ Practitioner(s) named below:

Name Registration Number

Place Customer Number Bar Code Label Here

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Address all telephone calls to Hal B. Woodrow at telephone number (732) 524-2976.

Direct all correspondence to: ☒ Customer Number or Bar Code Label 000027777 OR ☐ Correspondence address below

Name:		
Address:		
Address:		
City:	**State:**	**ZIP**
Country	**Telephone:**	**Fax:**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FIRST INVENTOR:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle [if any]) An	Family Name or Surname Vermeulen		
Inventor's Signature	Date		
Residence: City Beerse	State BE	Country BE	Citizenship BE
Mailing Address Turnhoutseweg 30			
City Beerse	State BE	ZIP	Country BE

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SECOND INVENTOR:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle [if any]) Alfons	Family Name or Surname Wouters		
Inventor's Signature	Date Mar 15 2009		
Residence: City Beerse	State BE	Country BE	Citizenship BE
Mailing Address Turnhoutseweg 30			
City Beerse	State BE	ZIP	Country BE

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF THIRD INVENTOR:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle [if any])	Family Name or Surname		
Inventor's Signature	Date		
Residence: City	State	Country	Citizenship
Mailing Address			
City	State	ZIP	Country

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.			
NAME OF SOLE OR FOURTH INVENTOR:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle [if any])	Family Name or Surname		
Inventor's Signature	Date		
Residence: City	State	Country	Citizenship
Mailing Address			
City	State	ZIP	Country
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.			
NAME OF FIFTH INVENTOR:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle [if any])	Family Name or Surname		
Inventor's Signature	Date		
Residence: City	State	Country	Citizenship
Mailing Address			
City	State	ZIP	Country
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.			
NAME OF INVENTOR:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle [if any])	Family Name or Surname		
Inventor's Signature	Date		
Residence: City	State	Country	Citizenship
Mailing Address			
City	State	ZIP	Country

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
12/337,144	12/17/2008	An Vermeulen	PRD2901USNP

CONFIRMATION NO. 3172

27777
PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

PUBLICATION NOTICE

OC000000036636855

Title:DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

Publication No.US-2009-0163519-A1
Publication Date:06/25/2009

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	An Vermeulen et al.	Confirmation No.	3172
Serial No.:	12/337,144	Group No.:	1614
Filed:	12/17/2008	Examiner:	Not Yet Assigned
For:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS		

CERTIFICATE OF EFS TRANSMISSION

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office on the date shown below via the "Electronic Filing System" in accordance with 37 C.F.R. § 1.6(a)(4).

Kristin Miele	/Kristin Miele/	January 21, 2010
Type or print name	Signature	Date

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

PETITION TO ACCEPT AN UNINTENTIONALLY DELAYED CLAIM OF PRIORITY

Sir:

The above-referenced patent application was filed on December 17, 2008 with a claim of priority that was not properly set forth. Applicants submit herewith a Preliminary Amendment Under 37 C.F.R. § 1.115 properly setting forth the proper relationship of the applications to which priority is claimed. Applicants respectfully submit that the entire delay between the date the claim was due under 37 C.F.R. 1.78(a)(6) and the date the claim was filed was unintentional.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

The Commissioner is hereby authorized to charge the required Petition fee of $1,410.00 to Deposit Account No. 10-0750/PRD2901USNP/HBW. (NOTE: all fees to be paid via EFS) The Commissioner is hereby authorized to charge any additional fees which may be required to Deposit Account No. 10-0750.

Respectfully submitted,

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
Phone: (732) 524-2976
Dated: January 21, 2010

By: /Hal Brent Woodrow/
Hal B. Woodrow, Reg. No. 32,501

CERTIFICATE OF EFS TRANSMISSION		
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office on the date shown below via the "Electronic Filing System" in accordance with 37 C.F.R. § 1.6(a)(4).		
Kristin Miele	/Kristin Miele/	January 21, 2010
Type or print name	Signature	Date

Docket No. PRD2901USNP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	An Vermeulen et al.	Confirmation No. 3172	
Serial No.:	12/337,144	Group No.:	1614
Filed:	12/17/2008	Examiner:	Not Yet Assigned
For:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS		

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

PRELIMINARY AMENDMENT

Sir:

Please amend the above-identified application as follows.

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 __ of this paper.

Remarks/Arguments begin on page 3 of this paper.

AMENDMENTS TO THE SPECIFICATION

Please insert the following new paragraph on Page 1, between the Title and line 4:

--CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U. S. Provisional Application 61/014,918, filed on December 19, 2007 and U. S. Provisional Application 61/120,276, filed on December 5, 2008.

REMARKS

Consideration of the captioned application in view of the foregoing amendments and following remarks is requested.

Amendments

The specification has been amended to refer to the priority applications.

CONCLUSION

The Commissioner is hereby authorized to charge any deficiency or credit any overpayments necessitated by this reply to Deposit Account No. 10-0750/PRD2901USNP/HBW.

Respectfully submitted,

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
Phone: (732) 524-2976
Dated: January 21, 2010

By: /Hal Brent Woodrow/
Hal B. Woodrow, Reg. No. 32,501

Electronic Patent Application Fee Transmittal

Application Number:	12337144
Filing Date:	17-Dec-2008
Title of Invention:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS
First Named Inventor/Applicant Name:	An Vermeulen
Filer:	Hal Brent Woodrow/Kristin Miele
Attorney Docket Number:	PRD2901USNP

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Priority accept. unintent. delayed claim	1454	1	1410	1410
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**1410**

Electronic Acknowledgement Receipt

EFS ID:	6853032
Application Number:	12337144
International Application Number:	
Confirmation Number:	3172
Title of Invention:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS
First Named Inventor/Applicant Name:	An Vermeulen
Customer Number:	27777
Filer:	Hal Brent Woodrow/Kristin Miele
Filer Authorized By:	Hal Brent Woodrow
Attorney Docket Number:	PRD2901USNP
Receipt Date:	21-JAN-2010
Filing Date:	17-DEC-2008
Time Stamp:	13:07:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1410
RAM confirmation Number	9926
Deposit Account	100750
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 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	Petition for review by the Office of Petitions.	PRD2901USNP_Petition_DelayedPriorityClaim.pdf	89178 42830a8f5e55945dda052482b6dcdade58bbd5bc	no	2
Warnings:					
Information:					
2		PRD2190USNP_PrelAmendment.pdf	229145 d44ccc9e0d3dc945df37eb6cc84daf7cf7bcc102	yes	3

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Preliminary Amendment	1	1
Specification	2	2
Applicant Arguments/Remarks Made in an Amendment	3	3

Warnings:					
Information:					
3	Fee Worksheet (PTO-875)	fee-info.pdf	30481 83ab15e96cb0dbf18dd061bf6a59433f5d837691	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	348804		

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.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/337,144	12/17/2008	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	330
☒ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	540
☒ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	220
TOTAL CLAIMS (37 CFR 1.16(i))	33 minus 20 =	* 13	X $ =		OR	X $52 =	676
INDEPENDENT CLAIMS (37 CFR 1.16(h))	6 minus 3 =	* 3	X $ =			X $220 =	660
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 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			TOTAL	2426

APPLICATION AS AMENDED – PART II

AMENDMENT 01/21/2010

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 33	Minus	** 33	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	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.

Legal Instrument Examiner:
/AJAY R. DAVID/

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Commissioner for Patents
United States Patent and Trademark Office
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Alexandria, VA 22313-1450
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PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK NJ 08933-7003

MAILED

MAR 2 9 2010

OFFICE OF PETITIONS

In re Application of
An Vermeulen et al.
Application No. 12/337,144
Filed: December 17, 2008
Attorney Docket No. PRD2901USNP

: DECISION ON PETITION
: UNDER 37 CFR 1.78(a)(6)

This is a decision on the petition under 37 CFR 1.78(a)(6), filed January 21, 2010, to accept an unintentionally delayed claim under 35 U.S.C. §119(e) for the benefit of prior-filed provisional applications 61/120,276 and 61/014,918, as set forth in the concurrently filed amendment.

The petition is **GRANTED**.

A petition under 37 CFR 1.78(a)(6) is only applicable to those applications filed on or after November 29, 2000. Further, the petition is appropriate only after expiration of the period specified in 37 CFR 1.78(a)(5)(ii) and must be filed during the pendency of the nonprovisional application. In addition, the petition must be accompanied by:

(1) the reference required by 35 U.S.C. § 119(e) and 37 CFR 1.78(a)(5)(i) to the prior-filed application, unless previously submitted;
(2) the surcharge set forth in § 1.17(t); and
(3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(5)(ii) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional.

Additionally, the instant nonprovisional application must be pending at the time of filing of the reference to the prior-filed provisional application as required by 37 CFR 1.78(a)(5)(iii). Further, the nonprovisional application claiming the benefit of the prior-filed provisional application must have been filed within twelve months of the filing date of the prior-filed provisional application.

All of the above requirements having been satisfied, the late claim for priority under 35 U.S.C. ***§119(e)*** is accepted as being unintentionally delayed.

The granting of the petition to accept the delayed benefit claim to the prior-filed application under 37 CFR 1.78(a)(6) should not be construed as meaning that the instant application is entitled to the benefit of the filing date of the prior-filed application. In order for the instant application to be entitled to the benefit of the prior-filed application, all other requirements under 35 U.S.C. §119(e) and 37 CFR 1.78(a)(4) and (a)(5) must be met. Similarly, the fact that the corrected Filing Receipt accompanying this decision on petition includes the prior-filed application should not be construed as meaning that applicant is entitled to the claim for benefit of priority to the prior-filed applications noted thereon. Accordingly, the examiner will, in due course, consider this benefit claim and determine whether the instant application is entitled to the benefit of the earlier filing date.

A corrected Filing Receipt, which includes the priority claim to the prior-filed provisional applications, accompanies this decision on petition.

Any inquiries concerning this decision may be directed to Senior Petitions Attorney Patricia Faison-Ball at (571) 272-3212. All other inquiries concerning either the examination procedures or status of the application should be directed to the Technology Center.

The application is being forwarded to Technology Center AU 1627 for consideration by the examiner of the claim under 35 U.S.C. §119(e) for the benefit of priority to the prior-filed provisional application.

Anthony Knight
Supervisor
Office of Petitions

ATTACHMENT: Corrected Filing Receipt

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	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/337,144	12/17/2008	1614	2426	PRD2901USNP	33	6

CONFIRMATION NO. 3172

27777
PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

FILING RECEIPT

OC00000003494024I

Date Mailed: 03/11/2009

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

An Vermeulen, Beerse, BELGIUM;
Alfons Wouters, Beerse, BELGIUM;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/014,918 12/19/2007
and claims benefit of 61/120,276 12/05/2008

Foreign Applications

If Required, Foreign Filing License Granted: 02/26/2009

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/337,144**

Projected Publication Date: 06/25/2009

Non-Publication Request: No

Early Publication Request: No

Title

DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

UNITED STATES PATENT AND TRADEMARK OFFICE

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Bib Data Sheet

CONFIRMATION NO. 3172

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/337,144	12/17/2008 RULE	514	1627	PRD2901USNP

APPLICANTS

An Vermeulen, Beerse, BELGIUM;
Alfons Wouters, Beerse, BELGIUM;

**** CONTINUING DATA ***************************

This appln claims benefit of 61/014,918 12/19/2007
and claims benefit of 61/120,276 12/05/2008

**** FOREIGN APPLICATIONS ********************

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 02/26/2009

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☐ no	BELGIUM	3	33	6

35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance

Verified and Acknowledged _____ Examiner's Signature Initials

ADDRESS
27777

TITLE

DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
2556	No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/337,144	12/17/2008	An Vermeulen	PRD2901USNP	3172

27777 7590 07/08/2010

PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

EXAMINER	
CLAYTOR, DEIRDRE RENEE	
ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
07/08/2010	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):

jnjuspatent@corus.jnj.com
lhowd@its.jnj.com
gsanche@its.jnj.com

Office Action Summary	Application No.	Applicant(s)	
	12/337,144	VERMEULEN ET AL.	
	Examiner	Art Unit	
	Renee Claytor	1627	

-- 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 *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *17 December 2008*.

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

3)☐ 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

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

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

8)☒ Claim(s) *1-34* are subject to restriction and/or election requirement.

Application Papers

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

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

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).

a)☐ All b)☐ Some * c)☐ None of:

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

This application contains claims directed to the following patentably distinct species of disorders that the psychiatric patient is being treated for. The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species of one mental disorder for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 12-15, 22-25 and 31-34 are generic.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a

claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim

remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Renee Claytor whose telephone number is (571)272-8394. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. 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.

/Shengjun Wang/
Primary Examiner, Art Unit 1627

Renee Claytor

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12337144	VERMEULEN ET AL.
	Examiner	**Art Unit**
	Renee Claytor	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/01/2010								
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CERTIFICATE OF TRANSMISSION

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office on the date shown below via Facsimile: 571-273-8300.

Hal B. Woodrow	/Hal Brent Woodrow/	9 August 2010
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: An Vermeulen et al. **Art Unit:** 1627

Serial No.: 12/337,144 **Examiner:** Claytor, D.

Filed: 12/17/2008 **Confirmation Number:** 3172

For: DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

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

RESPONSE TO ELECTION REQUIREMENT

Sir:

In response to the Office Action dated July 8, 2010 ("*Office Action*"), Applicants reply as follows.

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

Remarks/Arguments begin on page 16 of this paper.

AMENDMENTS TO THE CLAIMS

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

Listing of Claims:

1. (Original) A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

(1) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of from about 100mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(2) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment; and

(3) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

2. (Original) The method of claim 1 wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30th day of treatment.

3. (Original) The method of claim 1 wherein the sustained release formulation is an aqueous nanoparticle suspension.

4. (Original) A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of from about 100mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.

5. (Original) The method of claim 4 wherein the sustained release formulation is an aqueous nanoparticle suspension.

6. (Original) The method of claim 4 wherein the first loading dose is 150 mgs-eq. of paliperidone as paliperidone palmitate.

7. (Original) The method of claim 4 wherein the first loading dose is 100 mg-eq. of paliperidone as paliperidone palmitate.

8. (Original) The method of claim 4 wherein the second loading dose is 150 mg-eq. of paliperidone as paliperidone palmitate.

9. (Original) The method of claim 4 wherein the second loading dose is 100 mg-eq. of paliperidone as paliperidone palmitate.

10. (Original) The method of claim 4 wherein the first loading dose and the second loading dose are 150 mg-eq. of paliperidone as paliperidone palmitate.

11. (Original) The method of claim 4 wherein the first loading dose and the second loading dose are 150 mg of paliperidone as paliperidone palmitate.

12. (Original) The method of claim 4 wherein the psychiatric patient is in need of treatment for psychosis.

13. (Original) The method of claim 4 wherein the psychiatric patient is in need of treatment for schizophrenia.

14. (Original) The method of claim 4 wherein the psychiatric patient is in need of treatment for bipolar disorder.

15. (Original) The method of claim 4 wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with

Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Halluciogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with

Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7),

and Personality Disorders, Borderline (301.83).

17. (Original) A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6^{th} to about 10th day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

18. (Original) The method of claim 17 wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30^{th} day of treatment.

19. (Original) The method of claim 17 wherein the sustained release formulation is an aqueous nanoparticle suspension.

20. (Original) A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 50 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.

21. (Original) The method of claim 20 wherein the sustained release formulation is an aqueous nanoparticle suspension.

22. (Original) The method of claim 20 wherein the psychiatric patient is in need of treatment for psychosis.

23. (Original) The method of claim 4 wherein the psychiatric patient is in need of treatment for schizophrenia.

24. (Original) The method of claim 4 wherein the psychiatric patient is in need of treatment for bipolar disorder.

25. (Original) The method of claim 4 wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-

Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly

Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified

(298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

26. (Original) A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a maintenance dose of from about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

27. (Original) The method of claim 26 wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30th day of treatment.

28. (Original) The method of claim 26 wherein the sustained release formulation is an aqueous nanoparticle suspension.

29. (Original) A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a maintenance dose of from about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.

30. (Original) The method of claim 29 wherein the sustained release formulation is an aqueous nanoparticle suspension.

31. (Original) The method of claim 29 wherein the psychiatric patient is in need of treatment for psychosis.

32. (Original) The method of claim 29 wherein the psychiatric patient is in need of treatment for schizophrenia.

33. (Original) The method of claim 29 wherein the psychiatric patient is in need of treatment for bipolar disorder.

34. (Original) The method of claim 29 wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Halluciogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89),

Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia,

Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

REMARKS

In the Office Action, the Examiner has required an election of species.

Applicants acknowledge with thanks the discussion with the Examiner related to this application that occurred on August 9, 2010. Applicants' attorney understood from that discussion that it would be acceptable to elect for the claims to be initially examined for the treatment of schizophrenia and schizoaffective disease.

Accordingly, Applicants hereby elect the species of schizophrenia and schizoaffective diseases, (e.g. Schizophrenia Paranoid Type, Schizophrenia Disorganized, Schizophrenia Catatonic Type, Schizophrenia Undifferentiated Type, Schizophrenia Residual Type, Schizoaffective Disorder) described on lines 19-22 on page 19 of the specification, upon which claims 1-13, 15-23, 25-32 and 34 are readable. This election is without traverse to the extent that it is understood that (a) the requirement will be withdrawn upon the finding of an allowable genus; and (b) any species withdrawn from consideration will be transferred to the elected subject matter unless it is found patentably distinct from the elected or allowed claims.

With respect to the comments about 35 U.S.C. §121, Applicants' attorney respectfully submits that there has been no showing that all the conditions listed in the claims would require different fields of search (are in different classifications or would require different search queries) or that searching the claims would be unduly burdensome to the Examiner to qualify as a restriction under MPEP 803. The remaining rationale about different rejections being potentially present under 35 U.S.C. §101 and §112 is not a basis for restriction or election. This same arguments could apply to any claims no matter what the subject matter was, hence do not justify election or restriction requirements. Consequently, to the extent that the Office Action is intended to be a restriction requirement it is improper and does not comply with MPEP 803 or 35 U.S.C. §121.

CONCLUSION

Applicants respectfully request that consideration of claims 1-13, 15-23, 25-32 and 34 on the merits be commenced.

Attorney Docket No. PRD2901USNP

The Commissioner is hereby authorized to charge any deficiency or credit any overpayments necessitated by this reply to Deposit Account No. 10-0750/PRD2901USNP/HBW.

Respectfully submitted,

By: /Hal Brent Woodrow/
Hal B. Woodrow, Reg. No. 32,501

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
Phone: (732) 524-2976
Dated: 9 August 2010

Johnson & Johnson
CORPORATE HEADQUARTERS
PATENT LAW DEPARTMENT
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NEW JERSEY 08933

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FACSIMILE TRANSMISSION COVER SHEET

TO: **Examiner D. Renee Claytor**

COMPANY: **UNITED STATES PATENT & TRADEMARK OFFICE** COUNTRY: **U.S.A.**

FACSIMILE NUMBER: **571-273-8300**

FROM: **Hal B. Woodrow**

TELEPHONE NO.: **732-524-2976** ROOM NO.: **3232**

DATE: **August 9, 2010**

FACSIMILE NUMBER: **732-524-5889**

NUMBER OF PAGES INCLUDING THIS COVER SHEET: **18**
IF THERE IS A PROBLEM WITH THIS TRANSMISSION, PLEASE CALL
732-524-2820

COMMENTS:

Re: 12/337,144 Confirmation No. 3172
An Vermeulen et al.
Attorney Docket No. PRD 2901USNP

Dear Examiner Claytor,

Please find enclosed a Response for the above identified patent application.

Thank you.

Hal Woodrow

Hal B. Woodrow
32,501

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/337,144	12/17/2008	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			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 $250 ($125 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			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	08/09/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 33	Minus	** 33	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	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.

Legal Instrument Examiner:
/AJAY R. DAVID/

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27777 e 08/18/2010

PHILIP S. JOHNSON
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ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

Paper No.

Application No.:	**12/337,144**	**Date Mailed:**	**08/18/2010**
First Named Inventor:	Vermeulen, An,	Examiner:	CLAYTOR, DEIRDRE RENEE
Attorney Docket No.:	PRD2901USNP	Art Unit:	1627
Confirmation No.:	3172	Filing Date:	12/17/2008

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

Commissioner for Patents

PTO-90c (Rev.08-06)

Notice of Non-Compliant Amendment (37 CFR 1.121)	Application No. 12/337,144	Applicant(s) VERMEULEN ET AL.	
		Art Unit 1792	

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

The amendment document filed on *09 August, 2010* is considered non-compliant because it has failed to meet the requirements of 37 CFR 1.121 or 1.4. In order for the amendment document to be compliant, correction of the following item(s) is required.

THE FOLLOWING MARKED (X) ITEM(S) CAUSE THE AMENDMENT DOCUMENT TO BE NON-COMPLIANT:

- ☐ 1. Amendments to the specification:
  - ☐ A. Amended paragraph(s) do not include markings.
  - ☐ B. New paragraph(s) should not be underlined.
  - ☐ C. Other _____.
- ☐ 2. Abstract:
  - ☐ A. Not presented on a separate sheet. 37 CFR 1.72.
  - ☐ B. Other _____.
- ☐ 3. Amendments to the drawings:
  - ☐ A. The drawings are not properly identified in the top margin as "Replacement Sheet," "New Sheet," or "Annotated Sheet" as required by 37 CFR 1.121(d).
  - ☐ B. The practice of submitting proposed drawing correction has been eliminated. Replacement drawings showing amended figures, without markings, in compliance with 37 CFR 1.84 are required.
  - ☐ C. Other _____.
- ☒ 4. Amendments to the claims:
  - ☒ A. A complete listing of all of the claims is not present.
  - ☐ B. The listing of claims does not include the text of all pending claims (including withdrawn claims)
  - ☐ C. Each claim has not been provided with the proper status identifier, and as such, the individual status of each claim cannot be identified. Note: the status of every claim must be indicated after its claim number by using one of the following status identifiers: (Original), (Currently amended), (Canceled), (Previously presented), (New), (Not entered), (Withdrawn) and (Withdrawn-currently amended).
  - ☒ D. The claims of this amendment paper have not been presented in ascending numerical order.
  - ☒ E. Other: *Claim 16 is missing.*.
- ☐ 5. Other (e.g., the amendment is unsigned or not signed in accordance with 37 CFR 1.4): For further explanation of the amendment format required by 37 CFR 1.121, see MPEP § 714.

TIME PERIODS FOR FILING A REPLY TO THIS NOTICE:

1. Applicant is given **no new time period** if the non-compliant amendment is an after-final amendment or an amendment filed after allowance, or a drawing submission (only) If applicant wishes to resubmit the non-compliant after-final amendment with corrections, the **entire corrected amendment** must be resubmitted.

2. Applicant is given **one month**, or thirty (30) days, whichever is longer, from the mail date of this notice to supply the correction, if the non-compliant amendment is one of the following: a preliminary amendment, a non-final amendment (including a submission for a request for continued examination (RCE) under 37 CFR 1.114), a supplemental amendment filed within a suspension period under 37 CFR 1.103(a) or (c), and an amendment filed in response to a Quayle action. If any of above boxes 1 to 4 are checked, the correction required is only the corrected section of the non-compliant amendment in compliance with 37 CFR 1.121.

Extensions of time are available under 37 CFR 1.136(a) only if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action.

Failure to timely respond to this notice will result in:

Abandonment of the application if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action; or

Non-entry of the amendment if the non-compliant amendment is a preliminary amendment or supplemental amendment.

Legal Instruments Examiner (LIE), if applicable /Mamye Wagstaff/ Telephone No: 571-272-1057

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/337,144	12/17/2008	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			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 $250 ($125 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			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 08/09/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 33	Minus	** 33	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	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.

Legal Instrument Examiner:
/Mamye Wagstaff/

CERTIFICATE OF EFS TRANSMISSION		
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office on the date shown below via the "Electronic Filing System" in accordance with 37 C.F.R. § 1.6(a)(4).		
Kristin Miele	/Kristin Miele/	September 21, 2010
Type or print name	Signature	Date

In The United States Patent And Trademark Office

Applicants: An Vermeulen et al. **Art Unit:** 1627

Serial No.: 12/337,144 **Examiner:** Claytor, D.

Filed: 12/17/2008 **Confirmation Number:** 3172

For: DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

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

REPLY AND AMENDMENT

Sir:

In response to the Office Action dated July 8, 2010 ("*Office Action*") and the Notice of Non-Compliant Amendment dated August 18, 2010, Applicants reply as follows.

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

Remarks/Arguments begin on page 16 of this paper.

A one (1) month extension of time from September 18th 2010 to November 18th 2010 is respectfully requested for the filing of this response. The fee for such filing has been paid with the filing of this amendment.

Amendments to the Claims:

This listing of claims replaces all prior versions, and listings, of claims in the captioned application.

Listing of Claims:

1. (Original) A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

(1) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of from about 100mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(2) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6^{th} to about 10th day of treatment; and

(3) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

2. (Original) The method of claim 1 wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30^{th} day of treatment.

3. (Original) The method of claim 1 wherein the sustained release formulation is an aqueous nanoparticle suspension.

4. (Original) A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of from about 100mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.

5. (Original) The method of claim 4 wherein the sustained release formulation is an aqueous nanoparticle suspension.

6. (Original) The method of claim 4 wherein the first loading dose is 150 mgs-eq. of paliperidone as paliperidone palmitate.

7. (Original) The method of claim 4 wherein the first loading dose is 100 mg-eq. of paliperidone as paliperidone palmitate.

8. (Original) The method of claim 4 wherein the second loading dose is 150 mg-eq. of paliperidone as paliperidone palmitate.

9. (Original) The method of claim 4 wherein the second loading dose is 100 mg-eq. of paliperidone as paliperidone palmitate.

10. (Original) The method of claim 4 wherein the first loading dose and the second loading dose are 150 mg-eq. of paliperidone as paliperidone palmitate.

11. (Original) The method of claim 4 wherein the first loading dose and the second loading dose are 150 mg of paliperidone as paliperidone palmitate.

12. (Original) The method of claim 4 wherein the psychiatric patient is in need of treatment for psychosis.

13. (Original) The method of claim 4 wherein the psychiatric patient is in need of treatment for schizophrenia.

14. (Original) The method of claim 4 wherein the psychiatric patient is in need of treatment for bipolar disorder.

15. (Original) The method of claim 4 wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced

Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Halluciogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia

(292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89),

Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

16~~7~~. (Currently Amended) A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

17~~8~~. (Currently Amended) The method of claim 16~~7~~ wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30th day of treatment.

18~~9~~. (Currently Amended) The method of claim 16~~7~~ wherein the sustained release formulation is an aqueous nanoparticle suspension.

19~~20~~. (Currently Amended) A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 50 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.

201. (Currently Amended) The method of claim 1920 wherein the sustained release formulation is an aqueous nanoparticle suspension.

212. (Currently Amended) The method of claim 1920 wherein the psychiatric patient is in need of treatment for psychosis.

223. (Currently Amended) The method of claim 4 wherein the psychiatric patient is in need of treatment for schizophrenia.

234. (Currently Amended) The method of claim 4 wherein the psychiatric patient is in need of treatment for bipolar disorder.

245. (Currently Amended) The method of claim 4 wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80),

Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Halluciogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication

Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated

Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

25~~6~~. A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a maintenance dose of from about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 100 mg-

eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

26~~7~~. (Currently Amended) The method of claim 25~~6~~ wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30th day of treatment.

27~~8~~. (Currently Amended) The method of claim 25~~6~~ wherein the sustained release formulation is an aqueous nanoparticle suspension.

28~~9~~. (Currently Amended) A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a maintenance dose of from about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.

29~~30~~. (Currently Amended) The method of claim 28~~9~~ wherein the sustained release formulation is an aqueous nanoparticle suspension.

30~~1~~. (Currently Amended) The method of claim 28~~9~~ wherein the psychiatric patient is in need of treatment for psychosis.

312. (Currently Amended) The method of claim 289 wherein the psychiatric patient is in need of treatment for schizophrenia.

323. (Currently Amended) The method of claim 289 wherein the psychiatric patient is in need of treatment for bipolar disorder.

334. (Currently Amended) The method of claim 289 wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with

Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Halluciogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with

Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

REMARKS/ARGUMENTS

Claims 1-19 are pending. Claims 1-19 are subject to an election of species requirement.

In the Office Action, the Examiner has required an election of species.

Applicants acknowledge with thanks the discussion with the Examiner related to this application that occurred on August 9, 2010. Applicants' attorney understood from that discussion that it would be acceptable to elect for the claims to be initially examined for the treatment of schizophrenia and schizoaffective disease.

Accordingly, Applicants hereby elect the species of schizophrenia and schizoaffective diseases, (e.g. Schizophrenia Paranoid Type, Schizophrenia Disorganized, Schizophrenia Catatonic Type, Schizophrenia Undifferentiated Type, Schizophrenia Residual Type, Schizoaffective Disorder) described on lines 19-22 on page 19 of the specification, upon which claims 1-13, 15-23, 25-32 and 34 are readable. This election is without traverse to the extent that it is understood that (a) the requirement will be withdrawn upon the finding of an allowable genus; and (b) any species withdrawn from consideration will be transferred to the elected subject matter unless it is found patentably distinct from the elected or allowed claims.

With respect to the comments about 35 U.S.C. §121, Applicants' attorney respectfully submits that there has been no showing that all the conditions listed in the claims would require different fields of search (are in different classifications or would require different search queries) or that searching the claims would be unduly burdensome to the Examiner to qualify as a restriction under MPEP 803. The remaining rationale about different rejections being potentially present under 35 U.S.C. §101 and §112 is not a basis for restriction or election. This same arguments could apply to any claims no matter what the subject matter was, hence do not justify election or restriction requirements. Consequently, to the extent that the Office Action is intended to be a restriction requirement it is improper and does not comply with MPEP 803 or 35 U.S.C. §121.

Notice of Non-Compliant Amendment

Claims 17-34 have been amended to correct the sequential order of the claims, as numbered claim 16 was missing . Consequently, the status of claims 16-

33 has been amended accordingly. Applicants respectfully submit the Amendment is now compliant.

CONCLUSION

Applicants respectfully request that consideration of claims 1-13, 15-23, 25-32 and 34 on the merits be commenced. The Commissioner is hereby authorized to charge any deficiency or credit any overpayments necessitated by this Amendment to Deposit Account No. 10-0750/PRD2901USNP/HBW.

Respectfully submitted,

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
Phone: (732) 524-2976
Dated: 21 September 2010

By: /Hal Brent Woodrow/
Hal B. Woodrow, Reg. No. 32,501

Electronic Patent Application Fee Transmittal

Application Number:	12337144
Filing Date:	17-Dec-2008
Title of Invention:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS
First Named Inventor/Applicant Name:	An Vermeulen
Filer:	Hal Brent Woodrow/Kristin Miele
Attorney Docket Number:	PRD2901USNP

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

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:				
Extension - 1 month with $0 paid	1251	1	130	130

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**130**

Electronic Acknowledgement Receipt

EFS ID:	8462761
Application Number:	12337144
International Application Number:	
Confirmation Number:	3172
Title of Invention:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS
First Named Inventor/Applicant Name:	An Vermeulen
Customer Number:	27777
Filer:	Hal Brent Woodrow/Kristin Miele
Filer Authorized By:	Hal Brent Woodrow
Attorney Docket Number:	PRD2901USNP
Receipt Date:	21-SEP-2010
Filing Date:	17-DEC-2008
Time Stamp:	14:15:21
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$130
RAM confirmation Number	451
Deposit Account	100750
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 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		PRD2901USNP_Response_09_21_10.pdf	308181 34ba577d2764f2060488642e6d66290faa1fc5a7	yes	17

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	15
	Applicant Arguments/Remarks Made in an Amendment	16	17

Warnings:

Information:

2	Fee Worksheet (PTO-875)	fee-info.pdf	30626 5fed70bd860bd75c4a53d6e2acfad563d947329d	no	2

Warnings:

Information:

Total Files Size (in bytes):	338807

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.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. 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	Filing Date	☐ To be Mailed
12/337,144	12/17/2008	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			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 $250 ($125 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			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	09/21/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 33	Minus	** 33	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	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.

Legal Instrument Examiner:
/AJAY R. DAVID/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/337,144	12/17/2008	An Vermeulen	PRD2901USNP	3172

27777 7590 12/10/2010

PHILIP S. JOHNSON
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NEW BRUNSWICK, NJ 08933-7003

EXAMINER	
CLAYTOR, DEIRDRE RENEE	
ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
12/10/2010	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):

jnjuspatent@corus.jnj.com
lhowd@its.jnj.com
gsanche@its.jnj.com

Office Action Summary	Application No.	Applicant(s)	
	12/337,144	VERMEULEN ET AL.	
	Examiner	Art Unit	
	Renee Claytor	1627	

-- 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* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *21 September 2010*.

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

3)☐ 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

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *12,14,21,23,30 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11, 13, 15, 16-20, 22, 24-29, 31, 33* is/are rejected.

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

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

Application Papers

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

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

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).

a)☐ All b)☐ Some * c)☐ None of:

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

Applicant's election without traverse of the species of schizophrenia and schizoaffective diseases in the reply filed on 9/23/2010 is acknowledged.

Claims 1-11, 13, 15, 16-20, 22, 24-29, 31 and 33 are under examination herein as they read on the elected species.

Claim Rejections – 35 U.S.C. 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 13, 15, 16-20, 22, 24-29, 31 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of schizophrenia by the dosing regimen claimed, does not reasonably provide enablement for the treatment of all psychiatric disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547

the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

1. The nature of the invention and breadth of the claims: The claims are drawn to a dosing regimen for administering paliperidone palmitate to a psychiatric patient comprising (1) administering 150mg-eq. of paliperidone into the deltoid muscle on the first day of treatment (2) administering 100 mg-eq. of paliperidone into the deltoid muscle on the 6^{th} to 10^{th} day of treatment and (3) administering 25 mg-eq. of paliperidone to the deltoid muscle on the 34^{th} to 38^{th} day.

2. The state of the prior art: A review of the prior art indicates that paliperidone is prescribed for schizophrenia or schizoaffective diseases that all related to psychosis. On the other hand, claim 15 states that the psychiatric patient is in need of treatment for a mental disorder and a subsequent list of mental disorders such as Attention-Deficit/Hyperactivity Disorder (ADHD) and anxiety disorders to name only a couple. The treatment for ADHD includes stimulant medications such as methylphenidate and the treatment for anxiety disorders usually includes anti-depressant medications. This is an example that not all of the mental disorder conditions listed require the same types of treatment. Not all mental disorders will require an anti-psychotic for treatment.

3. The amount of direction or guidance presented and the presence or absence of working examples: Experiments in the specification teach pharmacokinetic profiles of gluteal versus deltoid intramuscular injections of paliperidone palmitate in patients with schizophrenia (see Examples 2- 8) according to the dosing regimen claimed. However, there are no examples of treatment of any other mental disorder with the anti-psychotic paliperidone, and especially according to the dosing regimen claimed.

4. The quantity of experimentation necessary: The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004). In the instant case, the art is very unpredictable as to using antipsychotic medications for the treatment of any mental disorder. Because little is known about the invention, the specification needs more detail as to how to treat all the various mental disorders listed with the anti-psychotic medication paliperidone and further, the specification would need detail as to how to treat mental disorders with paliperidone according to the dosing regimen claimed.

Claims 1-11, 13, 15, 16-20, 22, 24-29, 31 and 33 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims read on a dosing regimen for administering paliperidone palmitate to a psychiatric patient comprising (1) administering 150mg-eq. of paliperidone into the deltoid muscle on the first day of treatment (2) administering 100 mg-eq. of paliperidone into the deltoid muscle on the 6^{th} to 10^{th} day of treatment and (3) administering 25 mg-eq. of paliperidone to the deltoid muscle on the 34^{th} to 38^{th} day. There are various mental disorders listed which all have different etiologies, different symptoms and require different treatment regimens and there is no teaching that an anti-psychotic medication such as paliperidone will effectively treat all the various mental disorders listed such as ADHD, mental retardations or drug-induced hallucinations or dementias to name a few. There is a lack of written description for the entire breadth of the claims.

Conclusion

No claims are allowed.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Renee Claytor whose telephone number is (571)272-8394. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Renee Claytor

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12337144	VERMEULEN ET AL.
	Examiner	Art Unit
	Renee Claytor	1627

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
PALM Inventor Search	12/3/2010	RC
EAST	12/3/2010	RC

INTERFERENCE SEARCH			
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Bib Data Sheet

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/337,144	12/17/2008 RULE	514	1627	PRD2901USNP

APPLICANTS

An Vermeulen, Beerse, BELGIUM;
Alfons Wouters, Beerse, BELGIUM;

**** CONTINUING DATA **********

This appln claims benefit of 61/014,918 12/19/2007 and claims benefit of 61/120,276 12/05/2008

**** FOREIGN APPLICATIONS **********

IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 02/26/2009

		STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
Foreign Priority claimed	☐ yes ☒ no				
35 USC 119 (a-d) conditions met	☐ yes ☐ no ☐ Met after Allowance				
Verified and Acknowledged	/Renee Claytor/ RC Examiner's Signature Initials	BELGIUM	3	33	6

ADDRESS

27777

TITLE

DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

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2556	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12337144	VERMEULEN ET AL.
	Examiner	**Art Unit**
	Renee Claytor	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/01/2010	12/03/2010							
	1	÷	✓							
	2	÷	✓							
	3	÷	✓							
	4	÷	✓							
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	9	÷	✓							
	10	÷	✓							
	11	÷	✓							
	12	÷	N							
	13	÷	✓							
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	25	÷	✓							
	26	÷	✓							
	27	÷	✓							
	28	÷	✓							
	29	÷	✓							
	30	÷	N							
	31	÷	✓							
	32	÷	N							
	33	÷	✓							

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	414	paliperidone	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 14:00
S2	4	S1 and @ad="20071219"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 14:01
S3	169	S1 and @ad<="20071219"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 14:01
S4	37089	schizophren$2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 14:01
S5	93	S3 and S4	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 14:02
S6	9	dosing adj escalation	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 16:24
S7	0	S1 and S6	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 16:24
S8	31	"5254556"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 19:03
S9	19	"6077843"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 19:31
S10	11	"6555544"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 19:35
S11	20655	psychiatri$2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/12/03 10:28
S12	417	paliperidone	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/12/03 10:29
S13	139	S12 and S11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/12/03 10:29
S14	14	S11 same S12	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/12/03 10:29

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 6

Application Number	12/337,144
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First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Deirdre R. Claytor
Attorney Docket Number	PRD2901USNP

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.[1]	U.S. Patent Document Number	Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document mm-dd-yyyy	Pages, Columns, Lines, where relevant passages or relevant figures appear
		4,804,663		Kennis et al.	02-14-1989	
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		5,254,556		Janssen et al.	10-19-1993	
		5,453,425		Francois et al.	09-26-1995	
		5,612,346		Mesens et al.	03-18-1997	
		6,077,843		Fran.cedilla.ois et al.	06-20-2000	
		6,555,544		Fran.cedilla.ois et al.	04-29-2003	

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1 Unique citation designation number. 2 See attached Kinds of U.S. Patent Documents. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

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OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
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		ALPHS L, BOSSIE C, SLIWA JK, MA YW, HASKINS T TOLERABILITY OF PALIPERIDONE PALMITATE INITIATION DOSES IN SUBJECTS WITH RECENTLY DIAGNOSED SCHIZOPHRENIA. POSTER NO-NR6-21 AT THE 163RD ANNUAL MEETING OF THE AMERICAN PSYCHIATRIC ASSOCIATION (APA), NEW ORLEANS, LOUISIANA, USA, MAY 22-26, 2010.	
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Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 3 of 6

Application Number	12/337,144
Filing Date	12/17/08
First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Deirdre R. Claytor
Attorney Docket Number	PRD2901USNP

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No.[1]	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[2]
		GOPAL S, GASSMANN-MAYER C, PALUMBO J, SAMTANI MN, SHIWACH R, ALPHS L, PRACTICAL GUIDANCE FOR DOSING AND SWITCHING PALIPERIDONE PALMITATE TREATMENT IN PATIENTS WITH SCHIZOPHRENIA, CURRENT MEDICAL RESEARCH AND OPINION 26 (2), P.377-387, 2010	
		GOPAL S, HOUGH DW, XU H, LULL JM, GASSMANN-MAYER C, REMMERIE BM, EERDEKENS MH, BROWN DW, EFFICACY AND SAFETY OF PALIPERIDONE PALMITATE IN ADULT PATIENTS WITH ACUTELY SYMPTOMATIC SCHIZOPHRENIA: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-RESPONSE STUDY, INTERNATIONAL CLINICAL PSYCHOPHARMACOLOGY, pgs. 247-256 (2010)	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary) Sheet 4 of 6	*Application Number*	12/337,144
	Filing Date	12/17/08
	First Named Inventor	An Vermeulen
	Group Art Unit	1627
	Examiner Name	Deirdre R. Claytor
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		HOUGH D, GOPAL S, VIJAPURKAR U, LIM P, MOROZOVA M, EERDEKENS M, PALIPERIDONE PALMITATE IN PREVENTION OF SYMPTOM RECURRENCE IN PATIENTS WITH SCHIZOPHRENIA: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY, 161ST MEETING OF THE AMERICAN PSYCHIATRIC ASSOCIATION (APA), WASHINGTON, DC, USA, MAY 3-8, 2008, PROCEEDINGS/ABSTRACTBOOK, P.173, NO-NR4-029, 2008	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary) Sheet 5 of 6	*Application Number*	12/337,144
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	First Named Inventor	An Vermeulen
	Group Art Unit	1627
	Examiner Name	Deirdre R. Claytor
	Attorney Docket Number	PRD2901USNP

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Examiner's Initials*	Cite No.[1]	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[2]
		PANDINA GJ, LINDENMAYER JP, LULL J, LIM P, GOPAL S, KUSUMAKAR V, YUEN E, PALUMBO J A RANDOMIZED, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF THREE DOSES OF PALIPERIDONE PALMITATE IN ADULTS WITH AN ACUTE EXACERBATION OF SCHIZOPHRENIA. POSTER AT THE 12TH INTERNATIONAL CONGRESS ON SCHIZOPHRENIA RESEARCH (ICOSR), SAN DIEGO, CALIFORNIA, USA, MARCH 28 - APRIL 1, 2009.	
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		SAMTANI MN, GOPAL S, KERN SLIWA J, HASKINS T, ALPHS L, STUYCKENS K, VERMEULEN A PALIPERIDONE PALMITATE DOSING IN SPECIAL PATIENT POPULATIONS INCLUDING THE ELDERLY AND THOSE WITH RENAL IMPAIRMENT OR DIFFERING BODY MASS INDEX: GUIDANCE BASED ON PHARMACOKINETIC MODELING AND SIMULATION. POSTER AT THE AMERICAN CONFERENCE ON PHARMACOMETRICS, MASHANTUCKET, CONNECTICUT, USA, OCTOBER 4-7, 2009	

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OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No.[1]	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[2]
		SAMTANI MN, HASKINS JT, ALPHS L, SLIWA JK, STUYCKENS K, HERBEN V, VERMEULEN A MAINTENANCE DOSING OF ONCE-MONTHLY (4-WEEKLY) PALIPERIDONE PALMITATE IN SCHIZOPHRENIA: PHARMACOKINETIC RATIONALE BASED ON POPULATION SIMULATIONS. POSTER NO-21 AT THE 12TH ANNUAL MEETING OF THE COLLEGE OF PSYCHIATRIC AND NEUROLOGIC PHARMACISTS (CPNP), JACKSONVILLE, FLORIDA, APRIL 19-22, 2009.	
		SAMTANI MN, HASKINS JT, GOPAL S, SLIWA JK, ALPHS L, STUYCKENS K, VERMEULEN A DOSING INFORMATION FOR PALIPERIDONE PALMITATE - A ONCE-MONTHLY INJECTABLE ATYPICAL ANTIPSYCHOTIC - BASED ON POPULATION PHARMACOKINETIC ANALYSIS. POSTER NO-310 AT THE 22ND US PSYCHIATRIC AND MENTAL HEALTH CONGRESS (USPMHC), LAS VEGAS, NEVADA, USA, NOVEMBER 2-5, 2009.	
		SAMTANI MN, SLIWA JK, HASKINS JT, ALPHS L, STUYCKENS K, HERBEN V, VERMEULEN A INITIATION DOSING OF DELTOID INTRAMUSCULAR PALIPERIDONE PALMITATE IN SCHIZOPHRENIA: PHARMACOKINETIC RATIONALE BASED ON MODELING AND SIMULATION. POSTER NO-19 AT THE 12TH ANNUAL MEETING OF THE COLLEGE OF PSYCHIATRIC AND NEUROLOGIC PHARMACISTS (CPNP), JACKSONVILLE, FLORIDA, APRIL 19-22, 2009.	
		SAMTANI MN, VERMEULEN A, STUYCKENS K, POPULATION PHARMACOKINETICS OF INTRAMUSCULAR PALIPERIDONE PALMITATE IN PATIENTS WITH SCHIZOPHRENIA A NOVEL ONCE-MONTHLY, LONG-ACTING FORMULATION OF AN ATYPICAL ANTIPSYCHOTIC, CLINICAL PHARMACOKINETICS 48 (9), P.585-600, 2009.	
		SIKIRICA M, CRIVERA C, DIRANI R, COST-EFFECTIVENESS OF PALIPERIDONE PALMITATE VERSUS ORAL ATYPICALS IN THE US. POSTER NO-NR6-5 AT THE 163RD ANNUAL MEETING OF THE AMERICAN PSYCHIATRIC ASSOCIATION (APA), NEW ORLEANS, LOUISIANA, USA, MAY 22-26, 2010.	
		TURNER N, BOSSIE CA, HASKINS JT, KERN SLIWA J, MA YW, ALPHS L EFFECTS OF PALIPERIDONE PALMITATE IN ACUTELY ILL SUBJECTS WITH A MARKED TO SEVERE EXACERBATION OF SCHIZOPHRENIA. POSTER NO-NR6-26 AT THE 163RD ANNUAL MEETING OF THE AMERICAN PSYCHIATRIC ASSOCIATION (APA), NEW ORLEANS, LOUISIANA, USA, MAY 22-26, 2010.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Electronic Patent Application Fee Transmittal

Application Number:	12337144
Filing Date:	17-Dec-2008
Title of Invention:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS
First Named Inventor/Applicant Name:	An Vermeulen
Filer:	Hal Brent Woodrow/Kristin Miele
Attorney Docket Number:	PRD2901USNP

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

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($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	9857062
Application Number:	12337144
International Application Number:	
Confirmation Number:	3172
Title of Invention:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS
First Named Inventor/Applicant Name:	An Vermeulen
Customer Number:	27777
Filer:	Hal Brent Woodrow/Kristin Miele
Filer Authorized By:	Hal Brent Woodrow
Attorney Docket Number:	PRD2901USNP
Receipt Date:	11-APR-2011
Filing Date:	17-DEC-2008
Time Stamp:	20:58:12
Application Type:	Utility under 35 USC 111(a)

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Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	6515
Deposit Account	100750
Authorized User	

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Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 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	PRD2901USNP_IDS_04_11_11.pdf	285764 7f4708b4af171e6c105e4ce7efe7243106e9a6ed	no	4
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Filed (SB/08)	PRD2901USNP_IDS1449_04_11_11.pdf	380480 66c77a42decd216112dbf70d1094c12ccdf5d8c0	no	6
Warnings:					
Information:					
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3	NPL Documents	Alphs_05_22_10.pdf	86360 d85688fb09fdab3bc6b8b86f4ff0450da1d087ac	no	1
Warnings:					
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4	NPL Documents	Alphs_12_06_09.pdf	58014 4ebcce8176d67662068d6134a30f9f10ce4c0524	no	1
Warnings:					
Information:					
5	NPL Documents	Cleton_Assessment_04_02_2008.pdf	96374 a919d83c3693b2276dffbf15eca42fdc92bb66c2	no	1
Warnings:					
Information:					
6	NPL Documents	Coppola_03_17_10.pdf	167046 e68414cf9f9ce84a9826c3678ed62c9c01864377	no	1
Warnings:					
Information:					
7	NPL Documents	Gopal_05_20_10.pdf	102844 4fedac61d3453444a61e6806003b50189366ea98	no	1
Warnings:					
Information:					

8	NPL Documents	Gopal_377.pdf	285574 e0e31c310aaab822fc421eea16ebc6271920b5de	no	11
Warnings:					
Information:					
9	NPL Documents	Gopal_247.pdf	139465 6b2c86ede95bb9827ae0c9bcbc5fbc742c3ab29c	no	10
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Information:					
10	NPL Documents	Gopal_285S.pdf	3144747 d13ea6f368d184358556641e02569a505d9dcbe7	no	2
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Information:					
11	NPL Documents	Gopal_04_19_09.pdf	127734 d66add20ee4a131c2fa6ada20c0018d12b16178a	no	1
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Information:					
12	NPL Documents	Haskins_11_02_2009.pdf	27929 a181fa7a33cb2936bd2baac0fba481f5bcacb6bc	no	2
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Information:					
13	NPL Documents	Hough_05_01_08.pdf	111547 37d98cab124095c463450b229ce2f4b5b14944b5	no	1
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Information:					
14	NPL Documents	Hough_05_03_08.pdf	125670 988be0910db7bd3722e412e4887f9679941bbe32	no	1
Warnings:					
Information:					
15	NPL Documents	Hough_1022.pdf	1197552 ea52be1aa5d244d2ad68026ac5e0666ac74bc92b	no	10
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Information:					
16	NPL Documents	Kozma_05_22_10.pdf	8634536 189e7923c718bc1874a319bd7b5eeb37e2ba316c	no	6
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Information:					

17	NPL Documents	Kramer_05_03_08.pdf	86460 7e1bd6d2cceea18d3375cb18795cf878221 9de07	no	1
Warnings:					
Information:					
18	NPL Documents	Kramer_10_11_07.pdf	70143 9c0377383f520f05e8cd423bee5850b9140 8a465	no	7
Warnings:					
Information:					
19	NPL Documents	Pandina_12_06_09.pdf	123556 35d7b93f32b58cdbcdb3b0173a2cdf90c10 86f98	no	1
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20	NPL Documents	Pandina_03_28_09.pdf	193689 bdc46e7d7dac44618d91df3bbc2ad632f1e 4bff3	no	1
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Information:					
21	NPL Documents	Pandina_04_19_09.pdf	193768 0076bd39600bc341f0b73670a7a3ee603ac a9c96	no	1
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Information:					
22	NPL Documents	Samtani_Management_06_29_09.pdf	134996 1767f04a9e643e7368856b2f8a21f460db39 bd16	no	1
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Information:					
24	NPL Documents	Samtani_10_04_09.pdf	229011 07db7d3a413999fbde0bead1ce6f7444f21f 8b1d	no	1
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Information:					
25	NPL Documents	Samtani_Maintenance_04_19_09.pdf	417335 69ff8dce2c95ef3d153dd3818fd3191deb70 fd1b	no	1
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Information:					

26	NPL Documents	Samtani_11_02_2009.pdf	43712 f78bb8f209be2c36884abcf6cad4cd250d88bb22	no	2
Warnings:					
Information:					
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Information:					
28	NPL Documents	Samtani_585.pdf	281705 4addc3bb34cea9fab417a72549b939ac25a75e37	no	16
Warnings:					
Information:					
29	NPL Documents	Sikirica_05_22_10.pdf	147784 fbe3269452d9162b77ee70a2c57137d96ddb3602	no	6
Warnings:					
Information:					
30	NPL Documents	Turner_05_22_10.pdf	115733 6bd1b73c75d6e695c313aaa11656f63c74c339fe	no	6
Warnings:					
Information:					
31	Fee Worksheet (PTO-875)	fee-info.pdf	30601 fbe343b8fd01ced3e7b008a6671ab62bfda68d17	no	2
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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.

Docket No. PRD2901USNP

CERTIFICATE OF EFS TRANSMISSION		
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office on the date shown below via the "Electronic Filing System" in accordance with 37 C.F.R. § 1.6(a)(4).		
Kristin Miele	/Kristin Miele/	April 11, 2011
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: An Vermeulen et al. **Art Unit:** 1627

Serial No.: 12/337,144 **Examiner:** Claytor, D.

Filed: 12/17/2008 **Confirmation Number:** 3172

For: DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

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

INFORMATION DISCLOSURE STATEMENT

Dear Sir:

Pursuant to 37 C.F.R. §1.56 and in accordance with 37 C.F.R. §§1.97-1.98, information relating to the above-identified application is hereby disclosed. Inclusion of information in this statement is not to be construed as an admission that this information is material as that term is defined in 37 C.F.R. §1.56(b).

Applicant(s) reserve(s) the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist.

☐ In accordance with §1.97(b), since this Information Disclosure Statement is being filed either within three months of the filing date of the above-identified national application (other than a continued prosecution application under §1.53(d)), within three months of the date of entry into the national stage of the above identified application as set forth in §1.491, or before the mailing date of a first Office Action on the merits of the above-identified application, or before the mailing date of a first Office Action after the filing of a request for continued examination under §1.114, no additional fee is required.

☐ In accordance with §1.129(a), this Information Disclosure Statement is being filed in connection with ☐ the first or ☐ second After Final Submission, therefore:

- ☐ Statement in Accordance with §1.97(e) (attached); or
- ☐ Please charge Deposit Account No. 10-0750/ the fee of $180.00 as set forth in §1.17(p).

☒ In accordance with §1.97(c), this Information Disclosure Statement is being filed after the period set forth in §1.97(b) above but before the mailing date of either a Final Action under §1.113 or a Notice of Allowance under §1.311, or an action that otherwise closes prosecution and that it is accompanied by one of:

- ☐ Statement in Accordance with §1.97(e) (attached); or
- ☒ Please charge Deposit Account No. 10-0750/PRD2901USNP/HBW the fee of $180.00 as set forth in §1.17(p).

☐ In accordance with §1.97(d), this Information Disclosure Statement is being filed after the mailing date of either a Final Action under §1.113 or a Notice of Allowance under §1.311 but before the payment of the Issue Fee. Applicant(s) hereby petition(s) for consideration of this Information Disclosure Statement. Included are: Statement in Accordance with §1.97(e) as set forth below and the fee of $180.00 as set forth in §1.17(p).

☐ Copies of each of the references listed on the attached Form PTO-1449 are enclosed herewith.

☐ Copies of references listed on the attached Form PTO-1449 are enclosed herewith EXCEPT THAT:

- ☐ In view of the voluminous nature of references [list as appropriate], and the likelihood that these references are available to the Examiner, copies are not enclosed herewith.
- ☐ If any of the foregoing publications are not available to the Examiner, Applicant will endeavor to supply copies at the Examiner's request.

☒ Copies of only foreign patent documents and non-patent literature are enclosed in accordance with 37 CFR 1.98 (a)(2).

☒ There are no listed references which are not in the English language.

☐ The relevance of those listed references which are not in the English language is as follows:

☐ Attached are copies of search report(s) from corresponding patent application(s), which are listed on the attached Submission Under MPEP 609 D.

☐ Attached are the following non-published pending patent applications which may be deemed relevant, which are listed on the attached Submission Under MPEP 609 D.

Please charge any deficiency or credit any overpayment to Deposit Account No. 10-0750/PRD2901USNP/HBW.

Respectfully submitted,

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
Phone: (732) 524-2976
Dated: 11April 2011

By: /Hal Brent Woodrow/
Hal B. Woodrow, Reg. No. 32,501

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Attorney Docket No. PRD2901USNP

CERTIFICATE OF TRANSMISSION

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office on the date shown below via Facsimile: 571-273-8300.

Hal B. Woodrow	/Hal Brent Woodrow/	April 11, 2011
Type or print name	Signature	Date

In The United States Patent And Trademark Office

Applicants: An Vermeulen et al. **Art Unit:** 1627

Serial No.: 12/337,144 **Examiner:** Claytor, D. Renee

Filed: 12/17/2008 **Confirmation Number:** 3172

For: DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

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

REPLY AND AMENDMENT

Sir:

This paper is in response to the Office Action dated December 10, 2010, response to which is due, with a 1-month extension, on April 10, 2011. Appropriate extension of time request is contained in this paper.

Entry of the following amendment is respectfully requested.

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

Remarks/Arguments begin on page 16 of this paper.

EXTENSION OF TIME

It is requested that the period for filing a response to the present office action be extended one month to April 10, 2011. The Commissioner is hereby authorized to charge the extension fee of $130 .00 and any other fees that may be required by this paper to Deposit Account 10-0750/PRD2901USNP/HBW.

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Amendments to the Claims:

This listing of claims replaces all prior versions, and listings, of claims in the captioned application.

Listing of Claims:

1. (Original) A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

(1) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of from about 100mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(2) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment; and

(3) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

2. (Original) The method of claim 1 wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30th day of treatment.

3. (Original) The method of claim 1 wherein the sustained release formulation is an aqueous nanoparticle suspension.

PAGE 3/18 * RCVD AT 4/11/2011 5:46:25 PM [Eastern Daylight Time] * SVR:W-PTOFAX-001/45 * DNIS:2738300 * CSID:732 524 5889 * DURATION (mm-ss):03-53

4. (Original) A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of from about 100mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.

5. (Original) The method of claim 4 wherein the sustained release formulation is an aqueous nanoparticle suspension.

6. (Original) The method of claim 4 wherein the first loading dose is 150 mgs-eq. of paliperidone as paliperidone palmitate.

7. (Original) The method of claim 4 wherein the first loading dose is 100 mg-eq. of paliperidone as paliperidone palmitate.

8. (Original) The method of claim 4 wherein the second loading dose is 150 mg-eq. of paliperidone as paliperidone palmitate.

9. (Original) The method of claim 4 wherein the second loading dose is 100 mg-eq. of paliperidone as paliperidone palmitate.

10. (Original) The method of claim 4 wherein the first loading dose and the second loading dose are 150 mg-eq. of paliperidone as paliperidone palmitate.

11. (Original) The method of claim 4 wherein the first loading dose and the second loading dose are 150 mg of paliperidone as paliperidone palmitate.

12. (Withdrawn) The method of claim 4 wherein the psychiatric patient is in need of treatment for psychosis.

13. (Original) The method of claim 4 wherein the psychiatric patient is in need of treatment for schizophrenia.

14. (Canceled)

15. (Currently Amended) The method of claim 4 wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of ~~Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type-312.8), Oppositional Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81),~~

~~Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant Induced Mood Disorder (292.89), Inhalant Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance Induced Delirium (292.81), Other (or Unknown) Substance Induced Persisting Dementia (292.82), Other (or Unknown) Substance Induced Psychotic Disorder with Delusions~~

~~(292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2),~~ Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), ~~Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80),~~

~~Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).~~

16. (Previously Presented) A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

17. (Previously Presented) The method of claim 16 wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30th day of treatment.

18. (Previously Presented) The method of claim 16 wherein the sustained release formulation is an aqueous nanoparticle suspension.

19. (Previously Presented) A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 50 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.

20. (Previously Presented) The method of claim 19 wherein the sustained release formulation is an aqueous nanoparticle suspension.

21. (Withdrawn) The method of claim 19 wherein the psychiatric patient is in need of treatment for psychosis.

22. (Previously Presented) The method of claim 4 wherein the psychiatric patient is in need of treatment for schizophrenia.

23. (Canceled)

24. (Currently Amended) The method of claim 4 wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of ~~Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-~~

~~Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant Induced Anxiety Disorder (292.89), Inhalant Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting~~

~~Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance Induced Delirium (292.81), Other (or Unknown) Substance Induced Persisting Dementia (292.82), Other (or Unknown) Substance Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance Induced Mood Disorder (292.84), Other (or Unknown) Substance Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30),~~ Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief

Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), ~~Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), and Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).~~

25. (Previously Presented) A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a maintenance dose of from about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

26. (Previously Presented) The method of claim 25 wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30th day of treatment.

27. (Previously Presented) The method of claim 25 wherein the sustained release formulation is an aqueous nanoparticle suspension.

28. (Previously Presented) A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

(a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a maintenance dose of from about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.

29. (Previously Presented) The method of claim 28 wherein the sustained release formulation is an aqueous nanoparticle suspension.

30. (Withdrawn) The method of claim 28 wherein the psychiatric patient is in need of treatment for psychosis.

31. (Previously Presented) The method of claim 28 wherein the psychiatric patient is

in need of treatment for schizophrenia.

32. (Canceled)

33. (Currently Amended) The method of claim 28 wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of ~~Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol Induced Persisting Dementia (291.2), Alcohol Induced Psychotic Disorder with Delusions (291.5), Alcohol Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis Induced Psychotic Disorder with Delusions (292.11), Cannabis Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine Induced Psychotic Disorder with Delusions (292.11), Cocaine Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen Induced Psychotic disorder with Delusions (292.11),~~

~~Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance Induced Delirium (292.81), Other (or Unknown) Substance Induced Persisting Dementia (292.82), Other (or Unknown) Substance Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance Induced Mood Disorder (292.84), Other (or Unknown) Substance Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive~~

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Attorney Docket No. PRD2901USNP

REMARKS/ARGUMENTS

Claims 1-34 were originally filed in the present application. Claims 12, 21 and 30 are currently pending but withdrawn from consideration. Claims 16-34 were previously amended to correct the sequential order of the claims, as numbered claim 16 was missing . Claims 14, 23, and 32 are hereby cancelled. After entry of this amendment, claims 1-11, 13, 15, 16-20, 22, 24-29, 31 and 33 will be pending.

Claim Rejections Under 35 USC § 112

Claims 1-11, 13, 15, 16-20, 22, 24-29, 31 and 33 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement and written description requirement because the specification, while being enabling for and lacks written description for the treatment of schizophrenia by the dosing regimen claimed, does not reasonably provide enablement for the treatment of all psychiatric disorders.

Applicants' attorney respectfully specifically submits that these rejections are broader than the currently elected species and are improper. The election of species indicated the Examiner was going to examine the application for the indications of schizophrenia and schizoaffective disease. However the examination has now moved to all the indications in the claims and does not appear to be limited to the elected species. Is applicants' attorney to understand that the Examiner has found the elected species allowable and now has moved on to the remaining species in the application? If the Examine has found the originally elected species to be allowable Applicants attorney would like to have the claims to psychosis examined (e.g. 12, 20 and 30). Applicants attorney respectfully requests that the record be clarified as to the subject matter being examined.

Applicants' attorney respectfully submits that the present invention is fully enabled and satisfies the written description requirement. Antipsychotic compound are recognized by those skilled in the art to have a variety of uses including the treatment of the many ways in which psychosis may be manifest in patients which are currently claimed. The present compound is the major metabolite of risperidone and has been reported to have similar activity to risperidone with the advantage of not be metabolized to any significant degree in the liver. The activities of

compounds like risperidone and paliperidone that act on serotonin-$5HT_2$ and antagonize dopamine-D_2 are known in the art. Risperidone has been approved to treat schizophrenia and bipolar I disorder for acute mania and mixed episodes. However, paliperidone failed to separate from placebo in the treatment of bipolar disease in phase 3 trials. The failure of paliperidone in these trials may reflect more on the high placebo responses being seen in these clinical trials rather than a lack of efficacy of paliperidone. Additionally, antipsychotics have been reported to be useful to treat a variety of other indications such treatment resistant depression and anxiety in open label studies or case studies and many other disorders. Consequently, applicants' attorney submits that the previously presented claims were enabled and comply with the written description requirement. However, to expedite prosecution the claims have been amended to claim the treatment of psychosis, schizophrenia and closely related disorders (e.g. schizoaffective disease, schizophreniform disorder, etc.) facilitate allowance of the present application. Applicants' attorney reserves the right to pursue the deleted claims in a continuations at a later date.

CONCLUSION

Applicants respectfully request that consideration of claims 1-11, 13, 15, 16-20, 22, 24-29, 31 and 33 on the merits as well as withdrawn claims 12, 21 and 30. The Commissioner is hereby authorized to charge any deficiency or credit any overpayments necessitated by this Amendment to Deposit Account No. 10-0750/PRD2901USNP/HBW.

Respectfully submitted,

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
Phone: (732) 524-2976
Dated: April 11, 2011

By: /Hal Brent Woodrow/
Hal B. Woodrow, Reg. No. 32,501

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PATENT LAW DEPARTMENT
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NEW BRUNSWICK, NEW JERSEY 08933

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Attorney Docket No. PRD 2901USNP

Dear Examiner Claytor,

Please find enclosed a Response for the above identified patent application.

Thank you.

Hal B. Woodrow
32,501

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/337,144	12/17/2008	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
FOR	NUMBER FILED	NUMBER EXTRA					
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			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 $250 ($125 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			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	04/11/2011	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 30	Minus	** 33	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	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.

Legal Instrument Examiner:
/AJAY R. DAVID/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/337,144	12/17/2008	An Vermeulen	PRD2901USNP	3172

27777 7590 07/12/2011

PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

EXAMINER	
CLAYTOR, DEIRDRE RENEE	
ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
07/12/2011	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):

jnjuspatent@corus.jnj.com
lhowd@its.jnj.com
gsanche@its.jnj.com

Office Action Summary	Application No.	Applicant(s)
	12/337,144	VERMEULEN ET AL.
	Examiner	Art Unit
	Renee Claytor	1627

-- 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* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *11 April 2011*.

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

3)☐ 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

4)☒ Claim(s) *1-13,15-22,24-31 and 33* is/are pending in the application.

4a) Of the above claim(s) *12,21 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13,15-20,22,24-29,31 and 33* is/are rejected.

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

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

Application Papers

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

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

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).

a)☐ All b)☐ Some * c)☐ None of:

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/11/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants present arguments over the 35 USC 112 rejection over claims 1-11, 13, 15, 16-20, 22, 24-29, 31 and 33. In particular it is argued that the rejection is broader than the elected species and is improper. In order to clarify the record as requested by Applicants, all questions of enablement are evaluated against the claimed subject matter (see MPEP § 2164.08). Therefore, the rejection is proper in that it addresses the claims as a whole.

Applicants further argue that the invention is enabled. It is pointed out that the present compound is the major metabolite of risperidone and has been reported to have similar activity to risperidone. Applicants discuss the similar activities of both compositions and that antipsychotics have been useful in treating other indications such as depression and anxiety.

In response to the above arguments, it is noted that claim 1 for example, teaches administration of paliperidone to a psychiatric patient. The rejection is based on the fact that the instant specification is not enabled for the treatment of all psychiatric disorders. As admitted by Applicants in their response, risperidone is approved to treat schizophrenia and bipolar I disorder, paliperidone on the other hand fails to treat bipolar disorder. Therefore it is clear that paliperidone does not carry all of the same actions as risperidone and does not treat every psychiatric disorder. Therefore the rejection is maintained and given below.

Claim Rejections – 35 U.S.C. 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 13, 15, 16-20, 22, 24-29, 31 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of schizophrenia by the dosing regimen claimed, does not reasonably provide enablement for the treatment of all psychiatric disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

1. The nature of the invention and breadth of the claims: The claims are drawn to a dosing regimen for administering paliperidone palmitate to a psychiatric patient comprising (1) administering 150mg-eq. of paliperidone into the deltoid muscle

on the first day of treatment (2) administering 100 mg-eq. of paliperidone into the deltoid muscle on the 6th to 10th day of treatment and (3) administering 25 mg-eq. of paliperidone to the deltoid muscle on the 34th to 38th day.

2. The state of the prior art: A review of the prior art indicates that paliperidone is prescribed for schizophrenia or schizoaffective diseases that all related to psychosis. On the other hand, claim 15 states that the psychiatric patient is in need of treatment for a mental disorder and a subsequent list of mental disorders such as Attention-Deficit/Hyperactivity Disorder (ADHD) and anxiety disorders to name only a couple. The treatment for ADHD includes stimulant medications such as methylphenidate and the treatment for anxiety disorders usually includes anti-depressant medications. This is an example that not all of the mental disorder conditions listed require the same types of treatment. Not all mental disorders will require an anti-psychotic for treatment.

3. The amount of direction or guidance presented and the presence or absence of working examples: Experiments in the specification teach pharmacokinetic profiles of gluteal versus deltoid intramuscular injections of paliperidone palmitate in patients with schizophrenia (see Examples 2- 8) according to the dosing regimen claimed. However, there are no examples of treatment of any other mental disorder with the anti-psychotic paliperidone, and especially according to the dosing regimen claimed.

4. The quantity of experimentation necessary: The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches

how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004). In the instant case, the art is very unpredictable as to using antipsychotic medications for the treatment of any mental disorder. Because little is known about the invention, the specification needs more detail as to how to treat all the various mental disorders listed with the anti-psychotic medication paliperidone and further, the specification would need detail as to how to treat mental disorders with paliperidone according to the dosing regimen claimed.

Claims 1-11, 13, 15, 16-20, 22, 24-29, 31 and 33 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims read on a dosing regimen for administering paliperidone palmitate to a psychiatric patient comprising (1) administering 150mg-eq. of paliperidone into the

deltoid muscle on the first day of treatment (2) administering 100 mg-eq. of paliperidone into the deltoid muscle on the 6th to 10th day of treatment and (3) administering 25 mg-eq. of paliperidone to the deltoid muscle on the 34th to 38th day. There are various mental disorders listed which all have different etiologies, different symptoms and require different treatment regimens and there is no teaching that an anti-psychotic medication such as paliperidone will effectively treat all the various mental disorders listed such as ADHD, mental retardations or drug-induced hallucinations or dementias to name a few. There is a lack of written description for the entire breadth of the claims.

Conclusion

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.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Renee Claytor whose telephone number is (571)272-8394. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. 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.

Renee Claytor

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1627

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12337144	VERMEULEN ET AL.
	Examiner	**Art Unit**
	Renee Claytor	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/01/2010	12/03/2010	06/28/2011						
	1	÷	✓	✓						
	2	÷	✓	✓						
	3	÷	✓	✓						
	4	÷	✓	✓						
	5	÷	✓	✓						
	6	÷	✓	✓						
	7	÷	✓	✓						
	8	÷	✓	✓						
	9	÷	✓	✓						
	10	÷	✓	✓						
	11	÷	✓	✓						
	12	÷	N	N						
	13	÷	✓	✓						
	14	÷	N	-						
	15	÷	✓	✓						
	16	÷	✓	✓						
	17	÷	✓	✓						
	18	÷	✓	✓						
	19	÷	✓	✓						
	20	÷	✓	✓						
	21	÷	N	N						
	22	÷	✓	✓						
	23	÷	N	-						
	24	÷	✓	✓						
	25	÷	✓	✓						
	26	÷	✓	✓						
	27	÷	✓	✓						
	28	÷	✓	✓						
	29	÷	✓	✓						
	30	÷	N	N						
	31	÷	✓	✓						
	32	÷	N	-						
	33	÷	✓	✓						

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12337144	VERMEULEN ET AL.
	Examiner	**Art Unit**
	Renee Claytor	1627

SEARCHED			
Class	**Subclass**	**Date**	**Examiner**

SEARCH NOTES		
Search Notes	**Date**	**Examiner**
PALM Inventor Search	6/28/2011	RC
EAST (updated)	6/28/2011	RC

INTERFERENCE SEARCH			
Class	**Subclass**	**Date**	**Examiner**

PTO/SB/08A (08-00)
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Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 6

Application Number	12/337,144
Filing Date	12/17/08
First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Deirdre R. Claytor
Attorney Docket Number	PRD2901USNP

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.[1]	U.S. Patent Document Number	Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document mm-dd-yyyy	Pages, Columns, Lines, where relevant passages or relevant figures appear
		4,804,663		Kennis et al.	02-14-1989	
		5,158,952		Janssen et al.	10-27-1992	
		5,254,556		Janssen et al.	10-19-1993	
		5,453,425		Francois et al.	09-26-1995	
		5,612,346		Mesens et al.	03-18-1997	
		6,077,843		Fran.cedilla.ois et al.	06-20-2000	
		6,555,544		Fran.cedilla.ois et al.	04-29-2003	

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.[1]	Foreign Patent Document Office[3]	Number[4]	KindCode[5]	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document mm-dd-yyyy	Pages, Columns, Lines, where relevant passages or relevant figures appear	T[6]

Examiner Signature	/Renee Claytor/	Date Considered	/Renee Claytor/

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Unique citation designation number. 2 See attached Kinds of U.S. Patent Documents. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /R.C./

PTO/SB/08A (08-00)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 2 of 6

Application Number	12/337,144
Filing Date	12/17/08
First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Deirdre R. Claytor
Attorney Docket Number	PRD2901USNP

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No.[1]	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[2]
		ALPHS L, BOSSIE C, SLIWA JK, MA YW, HASKINS T TOLERABILITY OF PALIPERIDONE PALMITATE INITIATION DOSES IN SUBJECTS WITH RECENTLY DIAGNOSED SCHIZOPHRENIA. POSTER NO-NR6-21 AT THE 163RD ANNUAL MEETING OF THE AMERICAN PSYCHIATRIC ASSOCIATION (APA), NEW ORLEANS, LOUISIANA, USA, MAY 22-26, 2010.	
		ALPHS L, HASKINS, BOSSIE C, SLIWA JK, GOPAL S, HOUGH D, DAVIS J LONG-TERM METABOLIC OUTCOMES WITH PALIPERIDONE PALMITATE, A ONCE-MONTHLY LONG-ACTING INJECTABLE ANTIPSYCHOTIC AGENT, IN THE TREATMENT OF SUBJECTS WITH SCHIZOPHRENIA. POSTER NO-204 AT THE 48TH ANNUAL MEETING OF THE AMERICAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY (ACNP), HOLLYWOOD, FLORIDA, USA, DECEMBER 6-10, 2009.	
		CLETON A, ROSSENU S, CRAUWELS H, BERWAERTS J, HOUGH D, GOPAL S, EERDEKENS M, VANDEBOSCH A, ROSSO FERNANDEZ C ASSESSMENT OF THE DOSE PROPORTIONALITY OF PALIPERIDONE PALMITATE 25, 50, 100 AND 150 MG EQ., A NEW LONG-ACTING INJECTABLE ANTIPSYCHOTIC, FOLLOWING ADMINISTRATION IN THE DELTOID OR GLUTEAL MUSCLES. POSTER AT THE 2008 ANNUAL MEETING OF THE AMERICAN SOCIETY FOR CLINICAL PHARMACOLOGY AND THERAPEUTICS (ASCPT), ORLANDO, FLORIDA, USA, APRIL 2-5, 2008.	
		COPPOLA D, LIU Y, GOPAL S, REMMERIE B, SAMTANI M, PANDINA G, HOUGH D, NUAMAH I, SULAIMAN A LONG-TERM SAFETY, TOLERABILITY AND PHARMACOKINETICS OF PALIPERIDONE PALMITATE 234 MG (150 MG EQ.), THE HIGHEST MARKETED DOSE: A ONE-YEAR OPEN-LABEL STUDY IN PATIENTS WITH SCHIZOPHRENIA. POSTER NO-PI-49 AT THE 2010 ANNUAL MEETING OF THE AMERICAN SOCIETY FOR CLINICAL PHARMACOLOGY AND THERAPEUTICS (ASCPT), ATLANTA, GEORGIA, USA, MARCH 17-20, 2010.	
		GOPAL S, BERWAERTS J, NUAMAH I, AKHRAS K, COPPOLA D, DALY E, HOUGH DW, PALUMBO JM EFFICACY AND SAFETY OF LONG-ACTING INJECTABLE PALIPERIDONE PALMITATE RELATIVE TO LONG-ACTING HALOPERIDOL, BROMPERIDOL AND FLUPHENAZINE DECANOATE FOR LONG-TERM TREATMENT IN PATIENTS WITH SCHIZOPHRENIA USING NUMBER NEEDED TO TREAT AND NUMBER NEEDED TO HARM. POSTER AT THE 65TH ANNUAL CONVENTION AND SCIENTIFIC PROGRAM OF THE SOCIETY OF BIOLOGICAL PSYCHIATRY (SOBP), NEW ORLEANS, LOUISIANA, USA, MAY 20-22, 2010.	

Examiner Signature	/Renee Claytor/	Date Considered	/Renee Claytor/

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /R.C./

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(use as many sheets as necessary)

Sheet 3 of 6

Application Number	12/337,144
Filing Date	12/17/08
First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Deirdre R. Claytor
Attorney Docket Number	PRD2901USNP

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No.[1]	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[2]
		GOPAL S, GASSMANN-MAYER C, PALUMBO J, SAMTANI MN, SHIWACH R, ALPHS L, PRACTICAL GUIDANCE FOR DOSING AND SWITCHING PALIPERIDONE PALMITATE TREATMENT IN PATIENTS WITH SCHIZOPHRENIA, CURRENT MEDICAL RESEARCH AND OPINION 26 (2), P.377-387, 2010	
		GOPAL S, HOUGH DW, XU H, LULL JM, GASSMANN-MAYER C, REMMERIE BM, EERDEKENS MH, BROWN DW, EFFICACY AND SAFETY OF PALIPERIDONE PALMITATE IN ADULT PATIENTS WITH ACUTELY SYMPTOMATIC SCHIZOPHRENIA: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-RESPONSE STUDY, INTERNATIONAL CLINICAL PSYCHOPHARMACOLOGY, pgs. 247-256 (2010)	
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Examiner Signature	/Renee Claytor/	Date Considered	07/05/2011

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 4 of 6

Application Number	12/337,144
Filing Date	12/17/08
First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Deirdre R. Claytor
Attorney Docket Number	PRD2901USNP

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No.[1]	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[2]
		HOUGH D, GOPAL S, VIJAPURKAR U, LIM P, MOROZOVA M, EERDEKENS M, PALIPERIDONE PALMITATE IN PREVENTION OF SYMPTOM RECURRENCE IN PATIENTS WITH SCHIZOPHRENIA: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY, 161ST MEETING OF THE AMERICAN PSYCHIATRIC ASSOCIATION (APA), WASHINGTON, DC, USA, MAY 3-8, 2008, PROCEEDINGS/ABSTRACTBOOK, P.173, NO-NR4-029, 2008	
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Examiner Signature	/Renee Claytor/	Date Considered	07/05/2011

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Sheet 5 of 6

Application Number	12/337,144
Filing Date	12/17/08
First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Deirdre R. Claytor
Attorney Docket Number	PRD2901USNP

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No.[1]	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[2]
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Examiner Signature	/Renee Claytor/	Date Considered	07/05/2011

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Sheet 6 of 6

Application Number	12/337,144
Filing Date	12/17/08
First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Deirdre R. Claytor
Attorney Docket Number	PRD2901USNP

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Examiner Signature	/Renee Claytor/	Date Considered	07/05/2011

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /R.C./

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	12/337,144	Filing Date	2008-12-17	Docket Number (if applicable)	PRD2901USNP	Art Unit	1627
First Named Inventor	An Vermeulen			Examiner Name	Claytor, D. Renee		

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. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 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).

☐ 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.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☐ Other _____

☒ Enclosed

☐ Amendment/Reply

☒ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☒ Other
Response to Final Office Action to be filed under separate cover, via facsmile

MISCELLANEOUS

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

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 100750

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Hal Brent Woodrow/	Date (YYYY-MM-DD)	2011-12-12
Name	Hal. B. Woodrow	Registration Number	32501

This collection of information is required by 37 CFR 1.114. 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 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.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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 the Freedom of Information Act requires disclosure of these records.

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.

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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 inspections 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.

CERTIFICATE OF EFS TRANSMISSION		
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office on the date shown below via the "Electronic Filing System" in accordance with 37 C.F.R. § 1.6(a)(4).		
Kristin Miele	/Kristin Miele/	December 12, 2011
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: An Vermeulen et al. **Art Unit:** 1627

Serial No.: 12/337,144 **Examiner:** Claytor, D.

Filed: 12/17/2008 **Confirmation Number:** 3172

For: DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

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

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Dear Sir:

This copy is supplemental to the Information Disclosure Statement filed on April 11, 2011.

Pursuant to 37 C.F.R. §1.56 and in accordance with 37 C.F.R. §§1.97-1.98, information relating to the above-identified application is hereby disclosed. Inclusion of information in this statement is not to be construed as an admission that this information is material as that term is defined in 37 C.F.R. §1.56(b).

Applicant(s) reserve(s) the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist.

☒ In accordance with §1.97(b), since this Information Disclosure Statement is being filed either within three months of the filing date of the above-identified national application (other than a continued prosecution application under §1.53(d)), within three months of the date of entry into the national stage of the above identified application as set forth in §1.491, or before the mailing date of a first Office Action on the merits of the above-identified application, or before the mailing date of a first Office Action after the filing of a request for continued examination under §1.114, no additional fee is required.

☐ In accordance with §1.129(a), this Information Disclosure Statement is being filed in connection with ☐ the first or ☐ second After Final Submission, therefore:

- ☐ Statement in Accordance with §1.97(e) (attached); or
- ☐ Please charge Deposit Account No. 10-0750/ the fee of $180.00 as set forth in §1.17(p).

☐ In accordance with §1.97(c), this Information Disclosure Statement is being filed after the period set forth in §1.97(b) above but before the mailing date of either a Final Action under §1.113 or a Notice of Allowance under §1.311, or an action that otherwise closes prosecution and that it is accompanied by one of:

- ☐ Statement in Accordance with §1.97(e) (attached); or
- ☐ Please charge Deposit Account No. 10-0750/ the fee of $180.00 as set forth in §1.17(p).

☐ In accordance with §1.97(d), this Information Disclosure Statement is being filed after the mailing date of either a Final Action under §1.113 or a Notice of Allowance under

§1.311 but before the payment of the Issue Fee. Applicant(s) hereby petition(s) for consideration of this Information Disclosure Statement. Included are: Statement in Accordance with §1.97(e) (attached) and the fee of $180.00 as set forth in §1.17(p).

☐ Copies of each of the references listed on the attached Form PTO-1449 are enclosed herewith.

☐ Copies of references listed on the attached Form PTO-1449 are enclosed herewith EXCEPT THAT:

- ☐ In view of the voluminous nature of references [list as appropriate], and the likelihood that these references are available to the Examiner, copies are not enclosed herewith.
- ☐ If any of the foregoing publications are not available to the Examiner, Applicant will endeavor to supply copies at the Examiner's request.

☒ Copies of only foreign patent documents and non-patent literature are enclosed in accordance with 37 CFR 1.98 (a)(2).

☒ There are no listed references which are not in the English language.

☐ The relevance of those listed references which are not in the English language is as follows:

☐ Attached are copies of search report(s) from corresponding patent application(s), which are listed on the attached Submission Under MPEP 609 D.

☐ Attached are the following non-published pending patent applications which may be deemed relevant, which are listed on the attached Submission Under MPEP 609 D.

Please charge any deficiency or credit any overpayment to Deposit Account No. 10-0750/PRD2901USNP/HBW.

Respectfully submitted,

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
Phone: (732) 524-2976
Dated: 12 December 2011

By: /Hal Brent Woodrow/
Hal B. Woodrow, Reg. No. 32,501

PTO/SB/08A (08-00)
Approved for use through 10/31/2002. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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Sheet 1 of 4

Application Number	12/337,144
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First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Claytor, Deirdre
Attorney Docket Number	PRD2901USNP

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.[1]	U.S. Patent Document Number	Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document mm-dd-yyyy	Pages, Columns, Lines, where relevant passages or relevant figures appear
		6,577,545		Kim et al.	06/10/2003	
		2007/197591		Boom et al.	08/23/2007	

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.[1]	Foreign Patent Document Office[3]	Number[4]	KindCode[5]	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document mm-dd-yyyy	Pages, Columns, Lines, where relevant passages or relevant figures appear	T[6]
		WO	2006/114384		Janssen Pharmaceutica, NV	11/02/2006		

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 2 of 4

Application Number	12/337,144
Filing Date	12/17/2008
First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Claytor, Deirdre
Attorney Docket Number	PRD2901USNP

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No.[1]	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[2]
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		Alphs et al., "PALIPERIDONE PALMITATE VERSUS RISPERIDONE LONG-ACTING THERAPY IN MARKEDLY TO SEVERELY ILL SUBJECTS WITH SCHIZOPHRENIA", Poster presented at the 23rd Annual US Psychiatric and Mental Health Congress; Supported by Ortho-McNeil Janssen Scientific Affairs, LLC November 18–21, 2010; Orlando, FL, USA	
		Alphs et al., "Tolerability of Paliperidone Palmitate Initiation Doses in Subjects with Recently Diagnosed Schizophrenia", Poster handout presented at The Scientific Program of XXVII CINP Congress, Hong Kong. 6-10 June 2010.	
		Alphs et al., "Tolerability of Paliperidone Palmitate Initiation Doses in Subjects with Recently Diagnosed Schizophrenia", Poster presented at The Scientific Program of XXVII CINP Congress, Hong Kong. 6-10 June 2010.	
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		Gopal et al., "Efficacy and safety of paliperidone palmitate in adult patients with acutely symptomatic schizophrenia: a randomized, double-blind, placebo-controlled, dose-response study", International Clinical Psychopharmacology 2010, Vol 25 No 5, pgs. 247-256	

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Sheet 3 of 4

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Examiner Name	Claytor, Deirdre
Attorney Docket Number	PRD2901USNP

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
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		Samtani et al., "Dosing and Switching Strategies for Paliperidone Palmitate", CNS Drugs 2011; 25(10): 829-845	

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Sheet 4 of 4

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		Samtani et al., "Expansion of Paliperidone Palmitate Day 8 Dose Window from ± 2 Days to ± 4 Days: Model-Based Pharmacokinetic Simulation and Safety Data", Poster handout presented at the 24th Annual U.S. Psychiatric and Mental Health Congress Meeting, November 7-10, 2011, Las Vegas, Nevada	
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		Guidance Document: Patented Medicines (Notice of Compliance) Regulations, Health Canada, November 12, 2010	

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Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

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(54) Title: PREPARATION OF ASEPTIC 3-[2-[4-(6-FLUORO-1,2-BENZISOXAZOL-3-YL)-1-PIPERIDINYL]ETHYL]-6,7,8,9-TETRAHYDRO-9-HYDROXY-2-METHYL-4H-PYRIDIO[1,2-A]PYRIMIDIN-4-ONE PALMITATE ESTER

(57) Abstract: The present invention concerns a process for preparing aseptic crystalline 3-[2-[4- (6-fluoro-l,2-benzisoxazol-3-yl)-l-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy- 2-methyl-4H-pyrido[l,2-a]pyrimidin-4-one palmitate ester (I) substantially free of 3-[2-[4-(6-fluoro- 1 ,2-benzisoxazol-3-yl)- 1 -piperidinyl]ethyl]-6,7,8,9-tetrahydro-9- hydroxy-2-methyl-4H-pyrido[1 ,2-a] pyrimidin-4-one (II-a), 3-[2-[4-(6-fluoro-l ,2- benzisoxazol-3-yl)-l-piperidinyl]ethyl]-6,7-dihydro-2-methyl-4H-pyrido[l ,2-a]-pyrimidin-4-one (II-b), and 3-[2-[4-(6-fluoro-l,2-benzisoxazol-3-yl)-l-piperidinyl]- ethyl]-6,7,8,9-tetrahydro-2-methyl-9-pentadecyl-4H-pyrido[l ,2-a]pyrimidin-4-one (III), and having an average particle size ranging from 20 to 150 μm.

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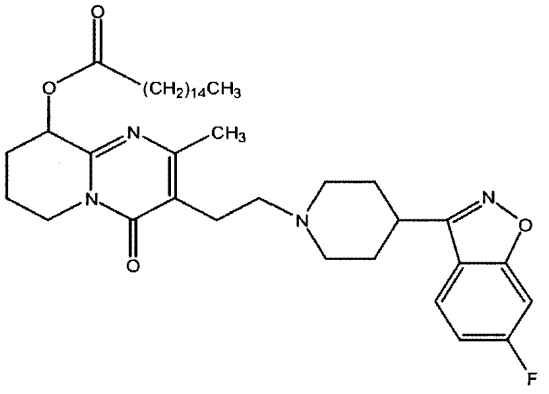
PREPARATION OF ASEPTIC 3-[2-[4-(6-FLUORO-1,2-BENZISOXAZOL-3-YL)-1-PIPERIDINYL]ETHYL]-6,7,8,9-TETRAHYDRO-9-HYDROXY-2-METHYL-4*H*-PYRIDO[1,2-a]PYRIMIDIN-4-ONE PALMITATE ESTER

Background of the invention

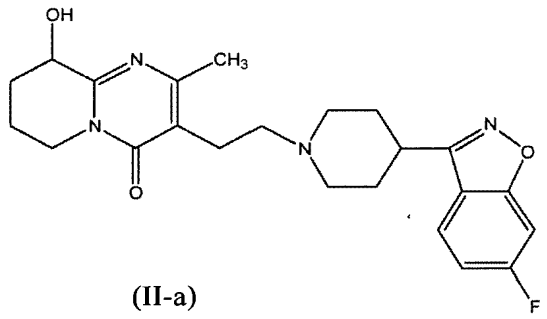
The present invention concerns a process for preparing aseptic crystalline 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one palmitate ester (I) substantially free of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (II-a), 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7-dihydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (II-b), and 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-9-pentadecyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (III), and having an average particle size ranging from 20 to 150 μm, preferably from 20 to 80 μm.

3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one palmitate ester (I) is also known as paliperidone palmitate ester; and the compound of formula (II-a) is also known as paliperidone.

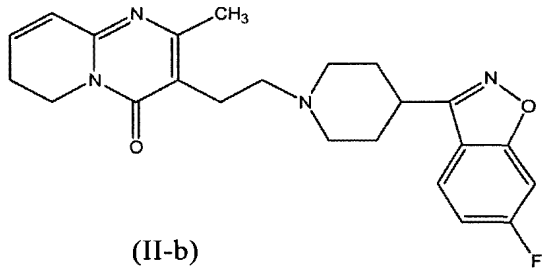
In EP-0,368,388 (US-5,158,952), 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one palmitate ester of formula (I) is disclosed.



EP-0,904,081 and EP-1,033,987 disclose aqueous suspensions of 'submicron' paliperidone palmitate (I) suitable as depot formulations which are therapeutically effective for about a month when administered intramuscularly to a warm-blooded subject. During pharmaceutical development, aseptic formulations of paliperidone palmitate (I) were initially obtained by gamma irradiation. Upon analysis of irradiated paliperidone (I), the process was found to give three breakdown products : up to 0.24 % of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (II-a) and 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7-dihydro-2-methyl-4*H*-pyrido[1,2-a]-pyrimidin-4-one (II-b) which in the analytical HPLC method co-eluted and are collectively designated (II) hereinafter,

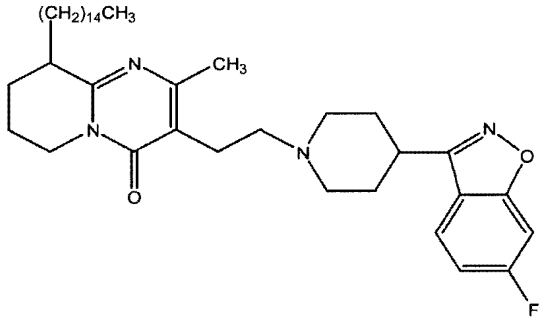


(II-a)



(II-b)

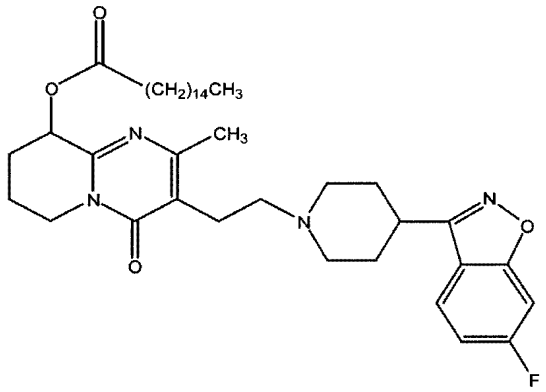
and up to 0.46 % of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-9-pentadecyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (III).



In order to avoid the formation of the breakdown products (II) [i.e. (II-a) and (II-b)] and (III), various other techniques to sterilize compound (I) were considered. Sterilization by microfiltration is impossible because the aqueous suspension of 'submicron'

paliperidone palmitate (I) will block the filter pores. Heat sterilization proves impossible as compound (I) melts between 116.5 and 119.5 °C.

The double objective of developing an aseptic production process for paliperidone palmitate (I) while managing its particle size distribution is achieved in the present invention which provides a process for preparing aseptic crystalline 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one palmitate ester of formula (I)



(I)

substantially free of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (II-a), 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7-dihydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (II-b) and 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-9-pentadecyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (III), and having an average particle size ranging from 20 to 150 μm, preferably from 20 to 80 μm,

comprising the steps of

a) heating 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one palmitate ester (I) and ethanol parenteral grade to 72 °C to 78 °C;

b) filtering the solution of step a) over a sterile 0.22 μm filter into a sterile crystallization reactor;

c) allowing 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one palmitate ester (I) to crystallize while cooling; and either

d) filtering off the thus obtained crystals; or

e) reheating the thus obtained suspension again to 72 °C to 78 °C;

f) allowing 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one palmitate ester (I) to crystallize while cooling; and

g) filtering off the thus obtained crystals.

The terms 'aseptic' and 'sterile' are used herein interchangeably and mean 'free or freed from micro-organisms'. All process steps following step b) are conducted aseptically under fully closed conditions applying isolator technology.

The process comprising the steps a), b), c), e), f) and g), that is the process comprising two heating cycles, is the more robust one as it allows the best control over the crystallization process and the particle size distribution of the particles.

The temperature achieved in step e) and the rate of cooling applied in step f) are particular important to the particle size distribution of aseptic paliperidone palmitate ester (I). Reheating to just below reflux temperature (< 77 °C) and cooling at a rate of 0.5 °C/min yields crystals having an average particle size of about 80 micron. Reheating to just below reflux temperature (< 77 °C) and cooling at a rate of 1 °C/min yields crystals having an average particle size of about 50 to 60 micron. In both instances, crystallization starts at about 60 °C. These conditions and parameters are equipment specific (here for a 30L reactor) and may vary when larger equipment is used.

Reheating to reflux temperature (78 °C) and rapid cooling yields crystals having an average particle size of about 20 to 30 micron. It is preferable that the rate of cooling in step f) is as rapid as possible.

Notwithstanding the aforementioned, a process comprising the steps a), b), c) and d), that is a process comprising only one heating cycle, is also feasible as can be seen from particular experiments in the experimental part.

In a further aspect of the invention, there is provided a process as described hereinbefore, comprising the further steps of
h) suspending the crystals obtained in steps d) or g) in a sterilized solution of water comprising a surfactant, and optionally a suspending agent and a buffer;
i) grinding the suspension of step h) in the presence of a grinding medium to particles having a specific surface area > 4 m^2/g;
j) sieving the suspension of step i) to remove the grinding medium;
k) diluting and mixing the solution of step j) with a sterilized solution of water optionally comprising a suspending agent, a buffer and an antioxidant; and
l) filling the sieved suspension into a sterile container.

These further process steps are known from EP-0,904,081 and EP-1,033,987.
In particular, the sterilized solution of water comprising a surfactant, and optionally a suspending agent and a buffer is prepared by dissolving a surfactant, and optionally a suspending agent and a buffer in water for injection and sterilizing the thus obtained solution by heating for 30 minutes at 121 °C, or by microfiltration. The grinding process is a wet milling process as disclosed in EP-0,499,299.

The particles of the present invention have a surfactant or surface modifier adsorbed on the surface thereof in an amount sufficient to maintain a specific surface area > 4 m^2/g (i.e. corresponding to an average particle size of less than 2,000 nm), preferably the specific surface area > 6 m^2/g, and in particular is in the range from 10 to 16 m^2/g. Useful surface modifiers are believed to include those which physically adhere to the surface of the active agent but do not chemically bond thereto.

Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface

modifiers include nonionic and anionic surfactants. Representative examples of excipients include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene allcyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available Tweens™, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminate silicate, triethanolamine, polyvinyl alcohol (PVA), poloxamers, tyloxapol and polyvinylpyrrolidone (PVP). Most of these excipients are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986. The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two or more surface modifiers can be used in combination.

Particularly preferred surface modifiers include polyvinylpyrrolidone; tyloxapol; poloxamers, such as Pluronic™ F68, F108 and F127 which are block copolymers of ethylene oxide and propylene oxide available from BASF; poloxamines, such as Tetronic™ 908 (T908) which is a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine available from BASF; dextran; lecithin; Aerosol OT™ (AOT) which is a dioctyl ester of sodium sulfosuccinic acid available from Cytec Industries; Duponol™ P which is a sodium lauryl sulfate available from DuPont; Triton™ X-200 which is an alkyl aryl polyether sulfonate available from Rohm and Haas; Tweens™ 20, 40, 60 and 80 which are polyoxyethylene sorbitan fatty acid esters available from ICI Speciality Chemicals; Span™ 20, 40, 60 and 80 which are sorbitan esters of fatty acids; Arlacel™ 20, 40, 60 and 80 which are sorbitan esters of fatty acids available from Hercules, Inc.; Carbowax™ 3550 and 934 which are polyethylene glycols available from Union Carbide; Crodesta™ F110 which is a mixture of sucrose stearate and sucrose distearate

available from Croda Inc.; Crodesta™ SL-40 which is available from Croda, Inc.; hexyldecyl trimethyl ammonium chloride (CTAC); bovine serum albumin and SA90HCO which is $C_{18}H_{17}CH_2$ $(CON(CH_3)CH_2(CHOH)_4CH_2OH)_2$. The surface modifiers which have been found to be particularly useful include tyloxapol and a poloxamer, preferably, Pluronic™ F108 and Pluronic™ F68, and polyoxyethylene sorbitan fatty acid esters, preferably Tween™ 20.

Pluronic™ F108 corresponds to poloxamer 338 and is the polyoxyethylene, polyoxypropylene block copolymer that conforms generally to the formula $HO[CH_2CH_2O]_x[CH(CH_3)CH_2O]_y[CH_2CH_2O)_zH$ in which the average values of x, y and z are respectively 128, 54 and 128. Other commercial names of poloxamer 338 are Hodag Nonionic™ 1108-F available from Hodag, and Synperonic™ PE/F108 available from ICI Americas.

The optimal relative amount of paliperidone palmitate and the surface modifier depends on various parameters. The optimal amount of the surface modifier can depend, for example, upon the particular surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, the surface area of (I), etc. The specific surface modifier preferably is present in an amount of 0.1 to 1 mg per square meter surface area of (I). In case Pluronic™ F108 is used as a surface modifier, a ratio (w/w) of (I) : surface modifier of approximately 6 : 1 is preferred. When Tween™ 20 is the surface modifier, a ratio (w/w) of (I) : surface modifier of approximately 13 : 1 is preferred.

As used herein, an effective average particle size of less than 2,000 nm means that at least 90 % of the particles have a diameter of less than 2,000 nm when measured by art-known conventional techniques, such as sedimentation field flow fractionation, photon correlation spectroscopy or disk centrifugation. With reference to the effective average particle size, it is preferred that at least 95 % and, more preferably, at least 99 % of the particles have a particle size of less than the effective average particle size, e.g. 2,000 nm. Most preferably, essentially all of the particles have a size of less than 2,000 nm.

The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in form having an average size less than 3 mm and, more preferably, less than 1 mm. Such media desirably can provide the particles of the invention with shorter processing times and impart less wear to the milling equipment. The selection of the material for the grinding media is believed not to be critical. However, 95 % ZrO stabilized with magnesia, zirconium silicate, and glass grinding media provide particles having levels of contamination which are believed to be acceptable for the preparation of pharmaceutical compositions. Further, other media, such as polymeric beads, stainless steel, titania, alumina and 95 % ZrO stabilized with yttrium, are useful. Preferred grinding media have a density greater than 2.5 g/cm3 and include 95 % ZrO stabilized with magnesia and polymeric beads.

The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected.

The particles must be reduced in size at a temperature which does not significantly degrade the antipsychotic agent. Processing temperatures of less than 30 to 40 °C are ordinarily preferred. If desired, the processing equipment may be cooled with conventional cooling equipment. The method is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process.

Aqueous compositions according to the present invention conveniently further comprise a suspending agent, a buffer and an antioxidant. Particular ingredients may function as two or more of these agents simultaneously, e.g. behave like a preservative and a buffer, or behave like a buffer and an isotonizing agent, or like a buffering agent and antioxidant.

Suitable suspending agents for use in the aqueous suspensions according to the present invention are cellulose derivatives, e.g. methyl cellulose, sodium carboxymethyl cellulose and hydroxypropyl methyl cellulose, polyvinylpyrrolidone, alginates, chitosan, dextrans, gelatin, polyethylene glycols, polyoxyethylene- and polyoxy-

propylene ethers. Preferably sodium carboxymethyl cellulose is used in a concentration of 0.5 to 2 %, most preferably 1 % (w/v). Suitable wetting agents for use in the aqueous suspensions according to the present invention are polyoxyethylene derivatives of sorbitan esters, e.g. polysorbate 20 and polysorbate 80, lecithin, polyoxyethylene- and polyoxypropylene ethers, sodium deoxycholate. Preferably polysorbate 20 is used in a concentration of 0.5 to 3 %, more preferably 0.5 to 2 %, most preferably 1.1 % (w/v).

Suitable buffering agents are salts of weak acids and should be used in amount sufficient to render the dispersion neutral to very slightly basic (up to pH 8.5), preferably in the pH range of 7 to 7.5. Particularly preferred is the use of a mixture of disodium hydrogen phosphate (anhydrous) (typically about 0.9 % (w/v)) and sodium dihydrogen phosphate monohydrate (typically about 0.6 % (w/v)). This buffer also renders the dispersion isotonic and, in addition, less prone to flocculation of the ester suspended therein. Citric acid is useful as an antioxidant.

Suitable sterile containers in which the suspension of paliperidone palmitate ester (I) may be filled comprise sterile holding vessels as well sterile syringes which then may packaged with appropriate needles into end-user packages.

The present invention also concerns aseptic crystalline 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one palmitate ester (I) substantially free of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (II-a), 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7-dihydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (II-b), and 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-9-pentadecyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (III), and having an average particle size ranging from 20 to 80 μm.

More in particular, the invention relates to aseptic crystalline 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-

pyrido[1,2-a]pyrimidin-4-one palmitate ester (I) containing less than 0.5 % of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (II-a), 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7-dihydro-2-methyl-4*H*-pyrido[1,2-a]-pyrimidin-4-one (II-b), and less than 0.01 % of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-9-pentadecyl-4*H*-pyrido[1,2-a]-pyrimidin-4-one (III), and having an average particle size ranging from 20 to 80 μm.

Further, the invention concerns aseptic crystalline 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]-pyrimidin-4-one palmitate ester (I) substantially free of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (II-a), 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7-dihydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (II-b), and 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-9-pentadecyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (III), and having a specific surface area > 4 m^2/g.

Experimental Part

Comparative Example

Compound (I) was irradiated with various doses of gamma rays in different containers. The amount of the breakdown products (II) [i.e. the sum of the amounts of compound (II-a) and (II-b)] and (III) increased dose-dependently.

Container	Dose (kGY)	(I)	(II)	(III)
Glass	0	99.0	-	-
	5	98.8	0.02	0.08
	10	98.7	0.05	0.15
	15	98.5	0.11	0.23
	20	98.3	0.17	0.34
	25	98.2	0.18	0.36
	30	98.0	0.24	0.46

Container	Dose (kGY)	(I)	(II)	(III)
Glass/metal	0	99.0	-	-
	5	98.8	0.02	0.08
	10	98.9	-	0.10
	15	98.5	0.11	0.23
	20	98.4	0.15	0.29
	25	97.2	0.05	0.35
	30	98.2	0.21	0.45
Plastic	0	99.0	-	-
	15	98.3	0.03	0.23
	20	97.9	0.03	0.29
	25	97.2	0.06	0.35

Example 1: GMP batches in pilot installation

All equipment was sterilized using the following techniques:

- steam sterilization
- dry heat sterilization
- vaporized hydrogen peroxide (VHP) sterilization
- gamma irradiation

To improve the sterility assurance of the process, all critical handlings with regard to sterility were performed in an isolator.

A reaction vessel was charged with 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one palmitate ester (2.5 kg) and ethanol parenteral grade (7 L/kg) and heated to reflux temperature (78 - 79 °C) while stirring. The product dissolved at about 70 °C. The solution was filtered at 76 °C over a sterile 0.22 μm filter into a glass crystallization reactor. The sterile filter was then washed with heated ethanol (1 L/kg).

The filtrate cooled to room temperature whereupon the product crystallized. The thus obtained suspension was either filtered off or reheated again.

Reheating to just below reflux temperature (< 77 °C) and cooling at a rate of 0.5 °C/min yielded crystals having an average particle size of about 80 micron. Reheating to just below reflux temperature (< 77 °C) and cooling at a rate of 1 °C/min yielded crystals having an average particle size of about 50 to 60 micron. In both instances, crystallization started at about 60 °C.

Reheating to reflux temperature (78 °C) and rapid cooling yielded crystals having an average particle size of about 20 to 30 micron.

The crystals were then filtered off, washed with ethanol parenteral grade (1 L/kg) and dried in vacuo at 50 °C in Tyvek bags so as to prevent dust formation.

HPLC analyses showed that the amount of the compound (I) was 99.4 % or more while the amount of (II-a) was 0.07 % or lower and compounds (II-b) and (III) were not detectable in any of the samples.

8 Batches were run, yielding product with a particle size distribution measured by laser diffraction as shown in Table 1.

Table 1

Run	Cooling rate	Crystallization						Particle size distribution			Yield (%)
		Calculated cooling gradient (°C/min)	Tmax	start cooling °C		start at (°C)		dl10 (μm)	dl50 (μm)	dl90 (μm)	
			Treactor	Tjacket	Treactor	Treactor	Tjacket				
1											
first crystallization	1°C/min	1.18	76	80	75.6	58	24.7	na	na	na	
second crystallization	1°C/min	1.01	75	80	75	61	29.3	244	73	18	89.7
2											
first crystallization	max	1.13	78	80	76	58	22	na	na	na	
second crystallization	max	1.13	77.5	80	73	50	13	95	29	9	95.2
3											
first crystallization	max	1.01	76.5	80	75	57.6	na	na	na	na	
second crystallization	max	1.01	78	80	77.5	46.7	na	104	20	7	96.2
4											
first crystallization	1°C/min	1.15	76.5	80	74	47	12.2	na	na	na	
second crystallization	1°C/min	1.01	76	80	74	61.9	28.1	285	82	19	73.4
5											
first crystallization	1°C/min	0.98	76	80	75	60.5	27.5	171	58	15	94.3
second crystallization	1°C/min	na	na	na	na	na	na	na	na	na	
6											
first crystallization	1°C/min	0.94	76	80	76	57	22	276	56	15	94.5
second crystallization	1°C/min	na	na	na	na	na	na	na	na	na	
7											
first crystallization	1°C/min	0.94	76	80	76	62	32	183	67	17	97.0
second crystallization	1°C/min	na	na	na	na	na	na	na	na	na	
8											
first crystallization	1°C/min	1.11	75.5	80	75	32	-4	na	na	na	
second crystallization	1°C/min	0.73	74	80	73	62	29	151	57	15	91.8

Example 2 : Scale up and equipment set upin Hastelloy C22 mini plant vessels of 30L, 60L and 160L.

A reactor was charged with 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]-pyrimidin-4-one palmitate ester and ethanol parenteral grade (8 L/kg) and heated to reflux temperature (78 - 79 °C) while stirring. The product dissolved at about 70 °C.

The reaction mixture is then cooled to room temperature whereupon the product crystallized. The thus obtained suspension was reheated again. The solution was cooled using differing cooling gradients (in consecutive experiments, the mixture was reheated and cooled again; after each cooling gradient, a sample was taken and isolated using a filter. The particle characteristics were determined.

HPLC analyses showed that the amount of (II-a) was 0.1 % or lower, and compounds (II-b) and (III) were not detectable in any of the samples.

Different batches were run, yielding product with a particle size distribution measured by laser diffraction as shown in Tables 2 to 4.

Table 2 : 30L scale experiments

Cooling rate	Crystallization					Particle size distribution		
	Calculated cooling gradient (°C/min)	Tmax Treactor	start at ... (°C) Treactor	Tjacket	start cooling (°C) Treactor	dl10 (µm)	dl50 (µm)	dl90 (µm)
1°C/min	1.04	79.7	25.8	24.7	79.6	647	12	3.6
max	8.95	77.5	56	-1	75.6	145	32	8.5
1°C/min	0.86	76.3	64.7	59.1	75.4	292	95	22
1°C/min	0.82	76.6	65.1	59.1	75.4	279	98	21
0.7°C/min	0.63	76.6	64.5	61	75.9	262	102	27
0.4°C/min	0.36	76.3	64.8	61.6	75.7	345	107	26

Table 3 : 60L scale experiments

Cooling rate	Crystallization					Particle size distribution		
	Calculated cooling gradient (°C/min)	Tmax Treactor	start at ... (°C)		start cooling (°C)	dl10 (µm)	dl50 (µm)	dl90 (µm)
			Treactor	Tjacket	Treactor			
0.4 °C/min	0.37	79.3	64.0	59.8	79.1	558.8	74.2	13.3
2.0 °C/min	1.42	79.6	60.4	44.5	75.0	805.3	44.4	9.3
0.7 °C/min	0.67	77.3	62.3	55.3	75.2	562.1	59.7	11.7
1.0 °C/min	0.81	78.9	61.9	52.3	74.9	562.7	52.0	10.6
1.0 °C/min	0.88	79.7	62.1	51.6	74.8	446.5	55.1	11.5

Table 4 : 160L scale experiments

Cooling rate	Crystallization					Particle size distribution		
	Calculated cooling gradient (°C/min)	Tmax Treactor	start at ... (°C)		start cooling (°C)	dl10 (µm)	dl50 (µm)	dl90 (µm)
			Treactor	Tjacket	Treactor			
1.0°C/min	1.0	78.6	60.1	42.4	78.4			
max	2.9	78.6	58.2	9	78.4	146	36	9.6
max	3.2	75.6	58	11	75.5	279	41	9.8
1.0°C/min	0.76	75.7	60.5	43.5	75.5	204	64	15
0.7°C/min	0.5	75.7	63	54	75.5	285	84	20
0.4°C/min	0.4	75.6	62.9	56.3	75.3	303	85	17
1°C/min	0.75	75.8	61.5	47.4	75.7	198	60	13

Example 3 : Crystallization in stainless steel reactor of 50L

All equipment was sterilized using dry heat sterilization.

A stainless steel reactor was charged with 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-*4H*-pyrido[1,2-a]-pyrimidin-4-one palmitate ester and ethanol parenteral grade (8 L/kg) and heated to reflux temperature (78 - 79 °C) while stirring. The product dissolved at about 70 °C.

The solution was filtered at 76 °C over a sterile 0.22 μm filter into a sterile crystallization reactor. The sterile filter was then washed with heated ethanol (1 L/kg).

The filtrate was reheated to reflux and then cooled to room temperature whereupon the product crystallized. The thus obtained suspension was reheated again. The solution was cooled using differing cooling gradients (in consecutive experiments, the mixture was reheated and cooled again; after each cooling gradient, a sample was taken and isolated using a filter. The crystals were dried in vacuo at 50 °C in Tyvek bags so as to prevent dust formation and the particle characteristics were determined.

Different batches were run, yielding product with a particle size distribution measured by laser diffraction as shown in Table 5.

Table 5

Cooling rate	Crystallization					Particle size distribution		
	Calculated cooling gradient (°C/min)	Tmax Treactor	start at ... (°C)		start cooling (°C)	dl10 (μm)	dl50 (μm)	dl90 (μm)
			Treactor	Tjacket	Treactor			
1 °C/min	0.95	78	63.5	60.2	77.5	156	65	16
ASAP	3.2	75.7	61.2	17.5	75	119	36	9.2
0.5 °C/min	0.48	75.7	63.8	62.7	75	192	80	20
0.5 °C/min	0.48	75.7	63.8	62.7	75	189	81	23
0.7 °C/min	0.81	75.7	61.7	58.9	75	113	41	11
1 °C/min	0.92	75.7	62.1	54.9	75	128	52	13

Example 4 : Preparation of finished form.

Composition

Table 6

Name	Amount Required			
	Per ml		Quantity for 24 L	
Paliperidone palmitate (sterile grade)	156	mg	3.744	kg
Polysorbate 20 parenteral	12	mg	288	g
Citric acid monohydrate parenteral	5	mg	120	g
Disodium hydrogen phosphate anhydrous parenteral	5	mg	120	g
Sodium dihydrogen phosphate monohydrate parenteral	2.5	mg	60	g
Sodium Hydroxide all use	2.84	mg	68	g
Polyethylene Glycol 4000 parenteral	30	mg	720	g
Water for injections q.s. ad	1000	µl	24	L

Equipment

- stainless steel (SS) containers
- Grinding media (Zirconium beads) + stainless steel (SS) grinding chamber
- 0.2 µm filters
- 40 µm filter
- Filling unit
- Autoclave
- Dry heat oven

Manufacturing

Zirconium beads wear cleaned and rinsed using water for injections and then depyrogenised by dry heat (120 min at 260°C). Water for injections was transferred into a SS container. Polysorbate 20 was added and dissolved by mixing. The solution was sterilized by filtration through a sterile 0.2 µm filter into a sterilized SS container. Paliperidone palmitate ester (sterile grade) as prepared in the previous examples was

dispersed into the solution and mixed until homogeneous. The suspension was milled aseptically in the grinding chamber using Zirconium beads as grinding media until the required particle size was reached. The suspension was filtered aseptically through a 40 µm filter into a sterilized SS container

Water for injections was transferred into a SS container, citric acid monohydrate parenteral, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide all use, polyethylene glycol 4000 were added and mixed until dissolved. This solution was sterilized by filtration through a sterile 0.2 µm filter and transferred aseptically into the suspension. The final suspension was mixed until homogeneous. The suspension was filled aseptically into sterile syringes. The target dose volume was between 0.25 ml and 1.50 ml depending on the dose needed.

Table 7

Dose volume	Target limit	lower limit	upper limit
0.25 ml - 1.00 ml	identical to dose volume	target limit – (target limit x 0.05)	target limit x 1.05
1.25 ml - 1.50 ml	identical to dose volume	target limit – (target limit x 0.025)	target limit x 1.025

Sterilization

All aseptic manipulations and sterilization processes were carried out according to FDA and European regulatory guidelines.

Apparatus

Sterilization was done by steam sterilization ($F_0 \geq 15$) of following equipment :

- SS containers
- Zirconium beads + grinding chamber
- 0.2 µm filters
- 40 µm filter
- filling pump

Immediate container

- 1 ml long transparent plastic (COC) syringe with luer lock.

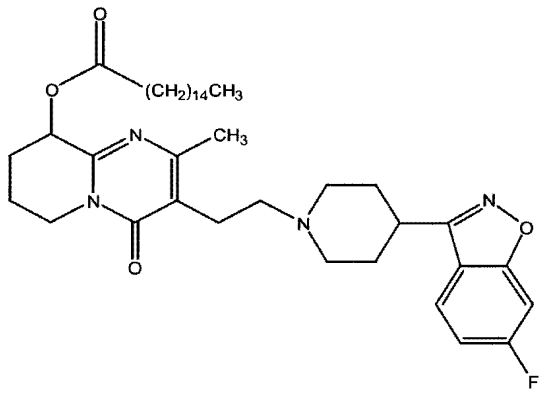
- rubber tip cap, FM257/2 dark grey
- rubber plunger stopper, 1 ml long, 4023/50, Flurotec B2-40

- 2.25ml transparent plastic (COC) syringe with luer lock.
- rubber tip cap, FM257/2 dark grey
- rubber plunger stopper, 1-3 ml, 4023/50, Flurotec B2-40

The empty syringes with pre-assembled tip-caps were sterilized by gamma-irradiation (dose ≥ 25 kGy). The rubber plunger stoppers were sterilized by means of steam sterilization ($F_0 \geq 15$).

Claims

1. A process for preparing aseptic crystalline 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido-[1,2-a]pyrimidin-4-one palmitate ester of formula (I)



(I)

substantially free of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (II-a), 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7-dihydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (II-b), and 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-9-pentadecyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (III), having an average particle size ranging from 20 to 150 μm, preferably from 20 to 80 μm,

comprising the steps of

a) heating 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-*4H*-pyrido[1,2-a]pyrimidin-4-one palmitate ester (I) and ethanol parenteral grade to 72 °C to 78 °C;

b) filtering the solution over a sterile 0.22 μm filter into a sterile crystallization reactor;

c) allowing 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one palmitate ester to crystallize while cooling; and either

d) filtering off the thus obtained crystals; or

e) reheating the thus obtained suspension again to 72 °C to 78 °C;

f) allowing 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one palmitate ester to crystallize while cooling; and

g) filtering off the crystals.

2. The process according to claim 1 comprising the steps a), b), c), e), f) and g).

3. The process according to claim 1 or 2 wherein the reheating in step e) is to reflux temperature.

4. The process according to claim 3 wherein the cooling in step f) is conducted as rapidly as possible.

5. The process according to claim 1 or 2 wherein the reheating step e) is conducted at < 77 °C.

6. The process according to claim 1 comprising the steps a), b), c) and d).

7. The process according to claim 1 comprising the further steps of

h) suspending the crystals obtained in steps d) or g) in a sterilized solution of water comprising a surfactant, a suspending agent and a buffer;

i) grinding the suspension of step h) in the presence of a grinding medium to particles having a specific surface area > 4 m^2/g;

j) sieving the suspension of step i) to remove the grinding medium;

k) diluting and mixing the solution of step j) with a sterilized solution of water optionally comprising a suspending agent, a buffer and an antioxidant; and

l) filling the sieved suspension into a sterile container.

8. Aseptic crystalline 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one palmitate ester (I) substantially free of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-

1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (II-a), 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7-dihydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (II-b), and 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-9-pentadecyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (III), and having an average particle size ranging from 20 to 150 μm.

9. Aseptic crystalline 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one palmitate ester (I) containing less than 0.5 % of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (II-a), 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7-dihydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (II-b), and less than 0.01 % of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-9-pentadecyl-4*H*-pyrido-[1,2-a]pyrimidin-4-one (III), and having an average particle size ranging from 20 to 150 μm.

10. Aseptic crystalline 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one palmitate ester (I) substantially free of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido-[1,2-a]pyrimidin-4-one (II-a), 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7-dihydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (II-b), and 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-9-pentadecyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (III), and having a specific surface area > 4 m^2/g.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/061694

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04

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)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/25354 A (JANSSEN PHARMACEUTICA N.V; FRANCOIS, MARC, KAREL, JOZEF; DRIES, WILLY,) 27 May 1999 (1999-05-27) page 11, line 7 - line 17; claim 2	1-9

☐ 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 document 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
28 August 2006	07/09/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Moriggi, J-D

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/061694

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9925354 A	27-05-1999	AP 1228 A	12-11-2003
		AT 239480 T	15-05-2003
		AU 745540 B2	21-03-2002
		AU 2049199 A	07-06-1999
		BG 104422 A	30-04-2001
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		DE 69814451 D1	12-06-2003
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		HK 1029045 A1	05-09-2003
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		ID 24981 A	31-08-2000
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		JP 2001522890 T	20-11-2001
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		PT 1033987 T	30-09-2003
		SK 6882000 A3	11-12-2000
		TR 200001282 T2	21-09-2000
		UA 72189 C2	15-09-2000
		US 2003064998 A1	03-04-2003
		ZA 9810467 A	16-05-2000

Electronic Patent Application Fee Transmittal

Application Number:	12337144
Filing Date:	17-Dec-2008
Title of Invention:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS
First Named Inventor/Applicant Name:	An Vermeulen
Filer:	Hal Brent Woodrow/Kristin Miele
Attorney Docket Number:	PRD2901USNP

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

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($)
Miscellaneous:				
Request for continued examination	1801	1	930	930
		Total in USD ($)		**930**

Electronic Acknowledgement Receipt

EFS ID:	11597815
Application Number:	12337144
International Application Number:	
Confirmation Number:	3172
Title of Invention:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS
First Named Inventor/Applicant Name:	An Vermeulen
Customer Number:	27777
Filer:	Hal Brent Woodrow/Kristin Miele
Filer Authorized By:	Hal Brent Woodrow
Attorney Docket Number:	PRD2901USNP
Receipt Date:	12-DEC-2011
Filing Date:	17-DEC-2008
Time Stamp:	17:19:53
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$930
RAM confirmation Number	4721
Deposit Account	100750
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	PRD2901USNP_RCE_12_12_11.pdf	697527 1fa124e60527ad125305e6c9dd0b28215f59c8ea	no	3
Warnings:					
Information:					
2	Transmittal Letter	PRD2901USNP_SupplIDS_12_12_11.pdf	286020 b5c36d72e65f8382538cc6ddc838f5c4f03aedb7	no	4
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	PRD2901USNP_SupplDS1449_12_12_11.pdf	300602 f96e6e3e61cb02aa0cacb31941735f74929eb592	no	4
Warnings:					
Information:					
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4	Foreign Reference	WO2006114384.pdf	1449422 541232ce2f851cd075e8051ec9e95880dc4d0352	no	25
Warnings:					
Information:					
5	Non Patent Literature	Alphs_poster_06_2010_HK.pdf	349009 6107ba54d8b9f56e42d79f0cc5a8ae8d43b0d2bd	no	1
Warnings:					
Information:					
6	Non Patent Literature	Alphs_poster_11_2010_OrlandoFL.pdf	959578 c8a3841e77a3c7ad57262f4d1d39de334d3df35a	no	6
Warnings:					
Information:					
7	Non Patent Literature	Alphs_poster_handout_06_2010_HK.pdf	664112 e86e581261f72b1aedc8ba1cb115948fc3cc520b	no	4
Warnings:					
Information:					

8	Non Patent Literature	Alphs_43.pdf	163094 418abaf10054e1f7cbfafa1806ce1074ba96e7a3	no	3
Warnings:					
Information:					
9	Non Patent Literature	Cleton.pdf	79538 ff8f3684f89c1c0a972ac8ad2e919456c42e5758	no	1
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Information:					
10	Non Patent Literature	Cockcroft.pdf	868642 6f84b96d0a756fa58a8741a3e1ac89f26ce38829	no	11
Warnings:					
Information:					
11	Non Patent Literature	Fleischhacker_1.pdf	965664 adcd02fc5bbf66d4ac28d3df3c5cf14b3bc8cddc	no	12
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12	Non Patent Literature	Gopal_247.pdf	972892 482a31b0bc277ea209130d969c0d3daa787c5129	no	10
Warnings:					
Information:					
13	Non Patent Literature	Gopal_NR1024_05_2011_Hawaii.pdf	201106 e348db0d6489473e405846db03215d7ef15f0db3	no	1
Warnings:					
Information:					
14	Non Patent Literature	Gopal_poster_06_2010_HK.pdf	1272061 adc2138b35cdf0a1e92d0b0febcc7278d86cc6fc	no	4
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Information:					
15	Non Patent Literature	Gopal_JPsychopharmacol_2010.pdf	268160 e71c1379bcdc5512fab32aad231d68cce532c06c	no	13
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Information:					
16	Non Patent Literature	Hough_1022.pdf	982248 ebd9a3096ee32d5350d685c8bc9096b952e8a6a2	no	10

Warnings:					
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17	Non Patent Literature	Hough_SchizRes_107.pdf	820936 d915037dd9befd4e785e45e8570ce637dcc3f058	no	11
Warnings:					
Information:					
18	Non Patent Literature	Li_poster_06_2010_HK.pdf	255101 21a2cf1800257ad02f9353f525db48f03f19ede0	no	1
Warnings:					
Information:					
19	Non Patent Literature	Nasrallah_2072.pdf	934881 0c4b9dcfdea3d257d6a445e02fc7a15455e20036	no	11
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Information:					
20	Non Patent Literature	Pandina_218.pdf	892358 8bc0e423b91e1f7fee652f2131eba84ad45bf039	no	9
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Information:					
21	Non Patent Literature	Pandina_235.pdf	999291 372528fa4e2190e0ea99ef65d2c5963f99c1a5db	no	10
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Information:					
22	Non Patent Literature	Revill.pdf	336837 f209ed25d8db5ed575d171d94a5154ec86554791	no	6
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Information:					
23	Non Patent Literature	Samtani_CNSDrugs_829.pdf	1813547 52dd0c9c8cd5727e7379e13ee1019aa468d22af6	no	17
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Information:					
24	Non Patent Literature	Samtani_poster_06_2010_Germany.pdf	406530 df90eccb6ff76b1b67579e944ff6de6b60c77cf2	no	1
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Information:					

25	Non Patent Literature	Samtani_poster_11_2011_Nevada.pdf	403062 441dc629df449e049113561aff77eedd01f7a05d	no	1
Warnings:					
Information:					
26	Non Patent Literature	Samtani_posterhandout_11_2011_Nevada.pdf	957043 83b0885e791b179972f86653277152efc8d7b912	no	4
Warnings:					
Information:					
27	Non Patent Literature	Samtani_presentation_10_2011.pdf	2096756 036fefaad4194c85810418ce443018acf7cf5099	no	15
Warnings:					
Information:					
28	Non Patent Literature	Sheehan_poster_06_2011_BocaRatonFL.pdf	375011 d6048c0f7451cfccb29a00fb69bcc590f7ee6824	no	1
Warnings:					
Information:					
29	Non Patent Literature	Sliwa_poster_04_2011_Colorado.pdf	920491 2ef0ede5a5707334f8a12592aa49260f97299115	no	6
Warnings:					
Information:					
30	Non Patent Literature	Ansels_2005.pdf	1081644 c801f108b59a9da66b65063cee3ed7c002eb36d4	no	9
Warnings:					
Information:					
31	Non Patent Literature	HealthCanada.pdf	240860 b7151d9b63621934736b4988da1d2c379f8f6230	no	4
Warnings:					
Information:					
32	Fee Worksheet (SB06)	fee-info.pdf	30545 96036d8f18dbe9757f4cbdded3b6abee0fb3f2ab	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	23044568	

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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.

Attorney Docket No. PRD2901USNP

CERTIFICATE OF TRANSMISSION

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office on the date shown below via Facsimile: 571-273-8300.

Hal B. Woodrow	/Hal Brent Woodrow/	12 December 2011
Type or print name	Signature	Date

In The United States Patent And Trademark Office

Applicants: An Vermeulen et al. **Art Unit:** 1627

Serial No.: 12/337,144 **Examiner:** Claytor, D. Renee

Filed: 12/17/2008 **Confirmation Number:** 3172

For: DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

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

REPLY AND AMENDMENT

Sir:

This paper is in response to the Office Action dated July 12, 2011, response to which is due, with a 2-month extension, on December 12, 2011. Appropriate extension of time request is contained in this paper.

Entry of the following amendment is respectfully requested.

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.

EXTENSION OF TIME

It is requested that the period for filing a response to the present office action be extended two months to December 12, 2011. The Commissioner is hereby authorized to charge the extension fee of $560.00 and any other fees that may be required by this paper to Deposit Account 10-0750/PRD2901USNP/HBW.

Amendments to the Claims:

This listing of claims replaces all prior versions, and listings, of claims in the captioned application.

Listing of Claims:

1. (Currently Amended) A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment schizophrenia, schizoaffective disorder, or schizophreniform disorder comprising

(1) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of ~~from~~ about ~~100mg eq. to about~~ 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(2) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of ~~from~~ about 100 mg-eq. ~~to about 150 mg-eq.~~ of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment; and

(3) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

2. (Original) The method of claim 1 wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30th day of treatment.

3. (Original) The method of claim 1 wherein the sustained release formulation is an aqueous nanoparticle suspension.

4. (Currently Amended) A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment for psychotic disorder comprising

(a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of ~~from about 100mg-eq. to~~ about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of ~~from~~ about 100 mg-eq. ~~to about 150 mg-eq.~~ of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.

5. (Original) The method of claim 4 wherein the sustained release formulation is an aqueous nanoparticle suspension.

6. (Cancelled)

7. (Cancelled)

8. (Cancelled)

9. (Cancelled)

10. (Cancelled)

11. (Cancelled)

12. (Cancelled)

13. (Currently Amended) The method of claim 4 wherein the psychiatric patient is in need of treatment for psychotic disorder wherein the psychotic disorder is schizophrenia.

14. (Canceled)

15. (Currently Amended) The method of claim 4 wherein the psychiatric patient is in need of treatment for a ~~mental~~ psychotic disorder wherein the psychotic disorder is schizoaffective disorder. ~~selected from the group consisting of Alcohol Induced Psychotic Disorder with Delusions (291.5), Alcohol Induced Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9)~~.

16. (Currently Amended) A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder comprising

(a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as

paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

17. (Previously Presented) The method of claim 16 wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30th day of treatment.

18. (Previously Presented) The method of claim 16 wherein the sustained release formulation is an aqueous nanoparticle suspension.

19. (Currently Amended) A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment for psychotic disorder comprising

(a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 50 mg-eq. of

paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.

20. (Previously Presented) The method of claim 19 wherein the sustained release formulation is an aqueous nanoparticle suspension.

21. (Cancelled)

22. (Currently Amended) The method of claim 4 wherein the psychiatric patient is in need of treatment for of a psychotic disorder wherein the psychotic disorder is schizophrenia.

23. (Canceled)

24. (Currently Amended) The method of claim 4 wherein the psychiatric patient is in need of treatment for a ~~mental~~ psychotic disorder wherein the psychotic disorder is schizoaffective disorder ~~selected from the group consisting of Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), and Psychotic Disorders Not Otherwise Specified (298.9),~~ .

25-33 (Cancelled)

REMARKS/ARGUMENTS

Status of the Claims

Claims 1-34 were originally filed in the present application. Claims 12, 21 and 30 are currently pending but withdrawn from consideration. Claims 1, 4, 13, 15, 16, 19, 22 and 24 have been amended. Claims 6-12, 14, 21, 23, and 25-33 are hereby cancelled. After entry of this amendment, claims 1-5, 13, 15-20, 22, and 24 will be pending.

Amendments to the Claims

Claims 1, 4, 13, 15, 16, 19, 22 and 24 have be amended to more clearly describe what applicants' invention. No new matter is added by these amendments. Entry and consideration of these amendments is respectfully requested.

Claims 6-12, 14, 21, 23, and 25-33 have been cancelled. However, applicants reserve the right to refile and pursue these claims in a later application. The cancellation of these claims is neither an admission of the correctness of any outstanding rejections or the surrender of the right to seek patent protection for this subject matter.

Response to comments

With regards to paliperidone and risperidone, applicants' attorney respectfully submits that paliperidone and risperidone share a very similar therapeutic profile. The applicants' attorney did report that in one study paliperidone failed to separate from placebo in the treatment of bipolar patients in the treatment of acute mania. However, this is not to say the paliperidone may not be effective for bipolar patients with acute mania. Rather this study showed a very pronounced treatment- by-country effect which confounded the interpretation of the study results. Other authors have reported that paliperidone is effective in the treatment of bipolar disorder. It is often the case that studies fail for reasons that may have little to do with the merit of the underlying drug. For example, risperidone failed in one of the three studies done for its approval to treat schizophrenia, yet no one would argue that risperidone is ineffective for the treatment of schizophrenia. Accordingly, applicants' attorney respectfully requests this basis for the rejection of the claims be

reconsidered. To facilitate the Examiner's review of this issue the relevant studies will be provided under a separate cover.

Response to the Rejections Under 35 USC § 112

Claims 1-11, 13, 15, 16-20, 22, 24-29, 31 and 33 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement because the specification, while being enabling for the treatment of schizophrenia by the dosing regimen claimed, does not reasonably provide enablement for the treatment of all psychiatric disorders. Applicants respectfully submit in view of the amendments to the claims that this rejection is now moot. Accordingly, reconsideration and withdrawal of this rejection is requested.

Paliperidone is known to have therapeutic activity mediated through a combination of central dopamine Type 2 (D2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism. Compounds that have activities at these receptors are recognized by those skilled in the art to be suitable for the treatment of a variety of mental illnesses including various forms of psychosis. See chapter 18 of Goodman & Gilman, The pharmacological Basis of Therapeutics, 11th Edition (2006). Goodman & Gilman also provides a list of conditions that are commonly treated with drugs which show D2-dopamine receptor activity. Both Goodman & Gilman 11th Edition (2006) and 12th Edition (2011) will be supplied to the Examiner in a separate filing. Even though the 12th Edition is not prior art per se it often cites papers that might be prior art.

Applicants' attorney, although not being an expert in the field, respectfully submits that once dosing is initiated with the described dosing regimen patients may be maintained on a therapeutically effective amount of the paliperidone palmitate as described in the specification on page 20, lines 3-16. Thus those skilled in the art will readily appreciate how to treat patients once the dosing regimen is started.

Accordingly, reconsideration and withdrawal of the rejection of claims 1-11, 13, 15, 16-20, 22, 24-29, 31 and 33 is respectfully requested.

Claims 1-11, 13, 15, 16-20, 22, 24-29, 31 and 33 rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. However, in view of the amendments to the claims, applicants'

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attorney respectfully submits that this rejection is moot. Accordingly, reconsideration of the claims is respectfully requested.

Goodman & Gilman 11th Edition and other publications provide those conditions that are generally treated with anti-psychotic agents. For example Goodman & Gilman 11th Edition describes conditions that are commonly treated with anti-psychotics beginning on page 481 and continuing through page 484. On page 483 there is a discussion of Special Populations that have been treated with anti-psychotics including those with delirium or dementia from a variety of causes.

Applicants' attorney respectfully submits that once the drug is administered as described a therapeutically effective level of drug is established in the patient and all that is required is maintenance treatments at about 1 month intervals. Maintenance dosing is as described on page 20, lines 3-16 of the specification. Those skilled in the art would readily be able to place a patient on an appropriate maintenance dose based on the teaching of the specification and the knowledge of those skilled in the art.

Accordingly, applicants' attorney respectfully requests reconsideration and withdrawal of the rejection of claims 1-11, 13, 15, 16-20, 22, 24-29, 31 and 33.

CONCLUSION

Applicants respectfully request reconsideration and allowance of claims 1-5, 13, 15-20, 22, and 24. The Commissioner is hereby authorized to charge any deficiency or credit any overpayments necessitated by this Amendment to Deposit Account No. 10-0750/PRD2901USNP/HBW.

Respectfully submitted,

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
Phone: (732) 524-2976
Dated: 12 December 2011

By: /Hal Brent Woodrow/
Hal B. Woodrow, Reg. No. 32,501

Johnson & Johnson
CORPORATE HEADQUARTERS
PATENT LAW DEPARTMENT
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NEW JERSEY 08933

FACSIMILE TRANSMISSION COVER SHEET

TO: **Examiner D. Renee Claytor**

COMPANY: **UNITED STATES PATENT & TRADEMARK OFFICE** COUNTRY: **U.S.A.**

FACSIMILE NUMBER: **571-273-8300**

FROM: **Hal B. Woodrow**

TELEPHONE NO.: **732-524-2976** ROOM NO.: **3232**

DATE: **December 12, 2011**

FACSIMILE NUMBER: **732-524-5889**

NUMBER OF PAGES INCLUDING THIS COVER SHEET: **10**
IF THERE IS A PROBLEM WITH THIS TRANSMISSION, PLEASE CALL
732-524-2820

COMMENTS:

Re: **12/337,144 Confirmation No. 3172**
An Vermeulen et al.
Attorney Docket No. PRD 2901USNP

Dear Examiner Claytor,

Please find enclosed a Response for the above identified patent application.

Thank you.

Hal B. Woodrow
32,501

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/337,144	12/17/2008	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			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 $250 ($125 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			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	12/12/2011									
	Total (37 CFR 1.16(i))	* 14	Minus	** 33	= 0	X $ =		OR	X $60=	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***6	= 0	X $ =		OR	X $250=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	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.

Legal Instrument Examiner:
/JACQUELINE COUPLIN/

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

27777 7590 06/25/2013

PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

EXAMINER
CLAYTOR, DEIRDRE RENEE

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 06/25/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/337,144	12/17/2008	An Vermeulen	PRD2901USNP	3172

TITLE OF INVENTION: DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$300	$0	$2080	09/25/2013

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: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (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)

27777 7590 06/25/2013
PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

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 facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/337,144	12/17/2008	An Vermeulen	PRD2901USNP	3172

TITLE OF INVENTION: DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$300	$0	$2080	09/25/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
CLAYTOR, DEIRDRE RENEE	1627	514-257000

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 03-02 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 has been filed for recordation as set forth in 37 CFR 3.11. 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. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27	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.
❑ Applicant changing to regular undiscounted fee 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: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information 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 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, 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.

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.
12/337,144	12/17/2008	An Vermeulen	PRD2901USNP	3172

27777 7590 06/25/2013

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NEW BRUNSWICK, NJ 08933-7003

EXAMINER	
CLAYTOR, DEIRDRE RENEE	
ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 06/25/2013

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 444 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 444 day(s).

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 Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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. 12/337,144	Applicant(s) VERMEULEN ET AL.	
	Examiner Renee Claytor	Art Unit 1627	AIA (First Inventor to File) Status No

-- 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 *the RCE filed on 12/12/2011*.
   ☐ 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 *1-5,13,15-20,22 and 24*. 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: _____.

   Interim copies:

   a) ☐ All b) ☐ Some c) ☐ None of the: Interim copies of the priority documents have been received.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply 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 _____
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 _____.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/12/2011 has been entered.

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 a telephone interview with Hal Woodrow on 6/14/2013.

The application has been amended as follows:

IN THE CLAIMS:

1. In claim 1, in line 2, after "a psychiatric patient in need of treatment" please insert "for".

2. In claim 2, in line 1, please delete "The method" and insert in its place "The dosing regimen".

3. In claim 3, in line 1, please delete "The method" and insert in its place "The dosing regimen".

4. In claim 5, in line 1, please delete "The method" and insert in its place "The dosing regimen".

5. In claim 13, in line 1, please delete "The method" and insert in its place "The dosing regimen".

6. In claim 15, in line 1, please delete "The method" and insert in its place "The dosing regimen".

7. In claim 17, in line 1, please delete "The method" and insert in its place "The dosing regimen".

8. In claim 18, in line 1, please delete "The method" and insert in its place "The dosing regimen".

9. In claim 20, in line 1, please delete "The method" and insert in its place "The dosing regimen".

10. In claim 22, in line 1, please delete "The method" and insert in its place "The dosing regimen".

11. In claim 24, in line 1, please delete "The method" and insert in its place "The dosing regimen".

The following is an examiner's statement of reasons for allowance: the prior art does not teach or suggest a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder or schizophreniform disorder comprising (1) administering i.m. in the deltoid a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; (2) administering i.m. in the deltoid a second loading dose of about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about the 10th day of treatment and (3) administering i.m. in the deltoid or gluteal muscle a maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

There was no prior art applied in this application. In addition, Applicant has enabled the present treatment method at least by Example 8 in the specification.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Renee Claytor whose telephone number is (571)272-8394. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. 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.

/Renee Claytor/
Primary Examiner, Art Unit 1627

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12337144	VERMEULEN ET AL.
	Examiner	Art Unit
	RENEE CLAYTOR	1627

CPC		
Symbol	Type	Version
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CPC Combination Sets				
Symbol	Type	Set	Ranking	Version
/				
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US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS
514	257

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
514	323	360	379		

INTERNATIONAL CLASSIFICATION

CLAIMED					NON-CLAIMED				
C	0	7	D	471 / 04 (2006.01.01)					
A	6	1	K	31 / 445 (2006.01.01)					
A	6	1	K	31 / 41 (2006.01.01)					
A	6	1	K	31 / 42 (2006.01.01)					

		Total Claims Allowed:	
NONE (Assistant Examiner)	(Date)	14	
/RENEE CLAYTOR/ Primary Examiner.Art Unit 1627 (Primary Examiner)	6/14/2013 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No. 20130614

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12337144	VERMEULEN ET AL.
	Examiner	**Art Unit**
	RENEE CLAYTOR	1627

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	14	
/RENEE CLAYTOR/ Primary Examiner.Art Unit 1627	6/14/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12337144	VERMEULEN ET AL.
	Examiner	**Art Unit**
	RENEE CLAYTOR	1627

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	9	17		33										
2	2	10	18												
3	3	11	19												
4	4	12	20												
5	5		21												
	6	13	22												
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	11		27												
	12		28												
6	13		29												
	14		30												
7	15		31												
8	16		32												

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	14	
/RENEE CLAYTOR/ Primary Examiner.Art Unit 1627	6/14/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12337144	VERMEULEN ET AL.
	Examiner	**Art Unit**
	Renee Claytor	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/01/2010	12/03/2010	06/28/2011	06/14/2013					
1	1	÷	✓	✓	=					
2	2	÷	✓	✓	=					
3	3	÷	✓	✓	=					
4	4	÷	✓	✓	=					
5	5	÷	✓	✓	=					
	6	÷	✓	✓	-					
	7	÷	✓	✓	-					
	8	÷	✓	✓	-					
	9	÷	✓	✓	-					
	10	÷	✓	✓	-					
	11	÷	✓	✓	-					
	12	÷	N	N	-					
6	13	÷	✓	✓	=					
	14	÷	N	-	-					
7	15	÷	✓	✓	=					
8	16	÷	✓	✓	=					
9	17	÷	✓	✓	=					
10	18	÷	✓	✓	=					
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	21	÷	N	N	-					
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	23	÷	N	-	-					
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	27	÷	✓	✓	-					
	28	÷	✓	✓	-					
	29	÷	✓	✓	-					
	30	÷	N	N	-					
	31	÷	✓	✓	-					
	32	÷	N	-	-					
	33	÷	✓	✓	-					

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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 4

Application Number	12/337,144
Filing Date	12/17/2008
First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Claytor, Deirdre
Attorney Docket Number	PRD2901USNP

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.[1]	U.S. Patent Document Number	Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document mm-dd-yyyy	Pages, Columns, Lines, where relevant passages or relevant figures appear
		6,577,545		Kim et al.	06/10/2003	
		2007/197591		Boom et al.	08/23/2007	

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.[1]	Foreign Patent Document Office[3]	Number[4]	KindCode[5]	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document mm-dd-yyyy	Pages, Columns, Lines, where relevant passages or relevant figures appear	T[6]
		WO	2006/114384		Janssen Pharmaceutica, NV	11/02/2006		

Examiner Signature	/Renee Claytor/	Date Considered	06/14/2013

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1 Unique citation designation number. 2 See attached Kinds of U.S. Patent Documents. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /R.C./

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 4

Application Number	12/337,144
Filing Date	12/17/2008
First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Claytor, Deirdre
Attorney Docket Number	PRD2901USNP

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No.[1]	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[2]
		Alphs et al., "Are the Long-Acting Intramuscular Formulations of Risperidone or Paliperidone Palmitate Associated with Post-Injection Delirium/Sedation Syndrome? An Assessment of Safety Databases", Current Drug Safety, 2011, 6, 43-45	
		Alphs et al., "PALIPERIDONE PALMITATE VERSUS RISPERIDONE LONG-ACTING THERAPY IN MARKEDLY TO SEVERELY ILL SUBJECTS WITH SCHIZOPHRENIA", Poster presented at the 23rd Annual US Psychiatric and Mental Health Congress; Supported by Ortho-McNeil Janssen Scientific Affairs, LLC November 18–21, 2010; Orlando, FL, USA	
		Alphs et al., "Tolerability of Paliperidone Palmitate Initiation Doses in Subjects with Recently Diagnosed Schizophrenia", Poster handout presented at The Scientific Program of XXVII CINP Congress, Hong Kong. 6-10 June 2010.	
		Alphs et al., "Tolerability of Paliperidone Palmitate Initiation Doses in Subjects with Recently Diagnosed Schizophrenia", Poster presented at The Scientific Program of XXVII CINP Congress, Hong Kong. 6-10 June 2010.	
		Cleton et al., Clinical Pharmacology & Therapeutics, Mosby-Year Book, St. Louis, MO, US, Vol. 81, No. Suppl. 1, page S63 (2007)	
		Cockcroft et al., Prediction of creatinine clearance from serum creatinine, Nephron, 16:31–41, 1976	
		Fleischhacker, W. Wolfgang et al., "A randomized trial of paliperidone palmitate and risperidone long-acting injectable in schizophrenia", International Journal of Neuropsychopharmacology, pgs. 1-12, CINP 2011	
		Gopal et al., "A 52-week open-label study of the safety and tolerability of paliperidone palmitate in patients with schizophrenia", *J Psychopharmacol.* 2010; First View: 1-13	
		Gopal et al., "Dosing Information for Paliperidone Palmitate—A Once-Monthly Injectable Atypical Antipsychotic—Based on Population Pharmacokinetic Analysis", Poster presented at The Scientific Program of XXVII CINP Congress, Hong Kong. 6-10 June 2010	
		Gopal et al., "Efficacy and safety of paliperidone palmitate in adult patients with acutely symptomatic schizophrenia: a randomized, double-blind, placebo-controlled, dose-response study", International Clinical Psychopharmacology 2010, Vol 25 No 5, pgs. 247-256	

Examiner Signature	/Renee Claytor/	Date Considered	06/14/2013

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 3 of 4

Application Number	12/337,144
Filing Date	12/17/2008
First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Claytor, Deirdre
Attorney Docket Number	PRD2901USNP

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No.[1]	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[2]
		Gopal et al., Risk of Cardiovascular Morbidity and Sudden Death with Risperidone and Paliperidone Treatment: Analysis of 64 Randomized, Double-Blind Trials, NR 10-24 Presented at the 164th Annual Meeting – American Psychiatric Association, May 14-18, 2011; Honolulu, Hawaii	
		Hough et al., "Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: A randomized, double-blind, placebo-controlled study", Schizophrenia Research 116 (2010) 107–117	
		Hough et al., "Safety and tolerability of deltoid and gluteal injections of paliperidone palmitate in schizophrenia", *Prog Neuropsychopharmacol Biol Psychiatry.* 2009;33:1022-1031	
		Li et al., "A Comparative Randomized, Open-label, Rater-blinded Study of Paliperidone Palmitate and Risperidone Long-Acting Injectable Therapy in Patients with Schizophrenia", Poster No. P-11-005 presented at the XXVII CINP Congress, June 06–10, 2010; Hong Kong	
		Nasrallah et al., "A Controlled, Evidence-Based Trial of Paliperidone Palmitate, A Long-Acting Injectable Antipsychotic, in Schizophrenia", Neuropsychopharmacology (2010) 35, 2072–2082	
		Pandina et al., "A double-blind study of paliperidone palmitate and risperidone long-acting injectable in adults with schizophrenia", Progress in Neuro-Psychopharmacology & Biological Psychiatry 2011:35:218-226	
		Pandina et al., "A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia", *J Clin Psychopharmacol.* 2010;30:235-244	
		Revill et al., Drugs of the Future, Prous Science, ES, Vol. 31, No. 7, pgs. 579-584 (2006)	
		Samtani et al., "Dosing and Switching Strategies for Paliperidone Palmitate", CNS Drugs 2011; 25(10): 829-845	

Examiner Signature	/Renee Claytor/	Date Considered	06/14/2013

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary) Sheet 4 of 4	*Application Number*	12/337,144
	Filing Date	12/17/2008
	First Named Inventor	An Vermeulen
	Group Art Unit	1627
	Examiner Name	Claytor, Deirdre
	Attorney Docket Number	PRD2901USNP

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Examiner's Initials*	Cite No.[1]	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[2]
		Samtani et al., "Expansion of Paliperidone Palmitate Day 8 Dose Window from ± 2 Days to ± 4 Days: Model-Based Pharmacokinetic Simulation and Safety Data", Poster presented at the 24th Annual U.S. Psychiatric and Mental Health Congress Meeting, November 7-10, 2011, Las Vegas, Nevada	
		Samtani et al., "Expansion of Paliperidone Palmitate Day 8 Dose Window from ± 2 Days to ± 4 Days: Model-Based Pharmacokinetic Simulation and Safety Data", Poster handout presented at the 24th Annual U.S. Psychiatric and Mental Health Congress Meeting, November 7-10, 2011, Las Vegas, Nevada	
		Samtani et al., "Switching to Paliperidone Palmitate[1,2] from Other Depot Antipsychotics Guidance Based on Pharmacokinetic Simulations", Population Approach Group in Europe, Applications-CNS (Group IV) Abstr 1839, Berlin, Germany. 8-11 June, 2010	
		Samtani, Mahesh N., "Use of Model Based Simulations to Support the Paliperidone Palmitate Label", AAPS Workshop on Facilitating Oral Product Development and Reducing Regulatory Burden through Novel Approaches to Assess Bioavailability/Bioequivalence, October 22-23, 2011, Washington	
		Sheehan et al., "The Management of Antipsychotic Treatment Discontinuation and Interruptions Using Model-Based Simulations", Poster presented at the 51st Annual NCDEU New Research Approaches for Mental Health Interventions Meeting, June 13-16, 2011, Boca Raton, Florida	
		Sliwa et al., "Tolerability and Efficacy of Paliperidone Palmitate vs Risperidone Long-acting Injection in Subjects with Recently Diagnosed Schizophrenia", Presented at the 13th International Congress on Schizophrenia Research; April 2-6, 2011; Colorado Springs, Colorado, USA	
		Alen et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 8th Edition, 2005; pgs. 260-263, 652-653, 682	
		Guidance Document: Patented Medicines (Notice of Compliance) Regulations, Health Canada, November 12, 2010	

Examiner Signature	/Renee Claytor/	Date Considered	06/14/2013

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12337144	VERMEULEN ET AL.
	Examiner	Art Unit
	Renee Claytor	1627

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	257, 323, 360, 379	6/14/2013	RC

SEARCH NOTES		
Search Notes	Date	Examiner
PALM Inventor Search	6/14/2013	RC
EAST (updated)	6/14/2013	RC

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
514	257, 323, 360, 379	6/14/2013	RC

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	414	paliperidone	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 14:00
S2	4	S1 and @ad="20071219"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 14:01
S3	169	S1 and @ad<="20071219"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 14:01
S4	37089	schizophren$2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 14:01
S5	93	S3 and S4	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 14:02
S6	9	dosing adj escalation	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 16:24
S7	0	S1 and S6	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 16:24
S8	31	"5254556"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 19:03
S9	19	"6077843"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 19:31
S10	11	"6555544"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 19:35
S11	20655	psychiatri$2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/12/03 10:28
S12	417	paliperidone	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/12/03 10:29
S13	139	S12 and S11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/12/03 10:29
S14	14	S11 same S12	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/12/03 10:29
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S16	185	S15 and @ad<="20071219"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2013/06/14 08:53
S17	46189	schizophren$2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2013/06/14 08:53
S18	102	S16 and S17	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2013/06/14 08:53
S19	102	S18	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2013/06/14 08:53

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	96	paliperidone	USPAT; UPAD	OR	OFF	2013/06/14 13:34

L2	12045	schizophren$2	USPAT; UPAD	OR	OFF	2013/06/14 13:34
L3	62	l1 and l2	USPAT; UPAD	OR	OFF	2013/06/14 13:35
L4	1647	514/257,323,360,379.ccls.	USPAT; UPAD	OR	OFF	2013/06/14 13:35
L5	1	l1 and l4	USPAT; UPAD	OR	OFF	2013/06/14 13:35

6/ 14/ 2013 1:35:32 PM
H:\ EASTBackup\ 337144.wsp

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	12/337,144	Filing Date	2008-12-17	Docket Number (if applicable)	PRD2901USNP	Art Unit	1627
First Named Inventor	An Vermeulen			Examiner Name	Claytor, D. Renee		

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. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 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).

☐ 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.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☐ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

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

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 100750

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Hal B. Woodrow/	Date (YYYY-MM-DD)	2013-09-17
Name	Hal. B. Woodrow	Registration Number	32501

This collection of information is required by 37 CFR 1.114. 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 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.

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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 inspections or an issued patent.

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CERTIFICATE OF EFS TRANSMISSION		
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office on the date shown below via the "Electronic Filing System" in accordance with 37 C.F.R. § 1.6(a)(4).		
Kristin Miele	/Kristin Miele/	September 18, 2013
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: An Vermeulen et al. **Art Unit:** 1627

Serial No.: 12/337,144 **Examiner:** Claytor, D.

Filed: 12/17/2008 **Confirmation Number:** 3172

For: DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

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

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Dear Sir:

This copy is supplemental to the Information Disclosure Statements filed on April 11, 2011 and December 12, 2011.

Pursuant to 37 C.F.R. §1.56 and in accordance with 37 C.F.R. §§1.97-1.98, information relating to the above-identified application is hereby disclosed. Inclusion of information in this statement is not to be construed as an admission that this information is material as that term is defined in 37 C.F.R. §1.56(b).

Applicant(s) reserve(s) the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist.

☒ In accordance with §1.97(b), since this Information Disclosure Statement is being filed either within three months of the filing date of the above-identified national application (other than a continued prosecution application under §1.53(d)), within three months of the date of entry into the national stage of the above identified application as set forth in §1.491, or before the mailing date of a first Office Action on the merits of the above-identified application, or before the mailing date of a first Office Action after the filing of a request for continued examination under §1.114, no additional fee is required.

☐ In accordance with §1.129(a), this Information Disclosure Statement is being filed in connection with ☐ the first or ☐ second After Final Submission, therefore:

- ☐ Statement in Accordance with §1.97(e) (attached); or
- ☐ Please charge Deposit Account No. 10-0750/ the fee of $180.00 as set forth in §1.17(p).

☐ In accordance with §1.97(c), this Information Disclosure Statement is being filed after the period set forth in §1.97(b) above but before the mailing date of either a Final Action under §1.113 or a Notice of Allowance under §1.311, or an action that otherwise closes prosecution and that it is accompanied by one of:

- ☐ Statement in Accordance with §1.97(e) (attached); or
- ☐ Please charge Deposit Account No. 10-0750/ the fee of $180.00 as set forth in §1.17(p).

☐ In accordance with §1.97(d), this Information Disclosure Statement is being filed after the mailing date of either a Final Action under §1.113 or a Notice of Allowance under

§1.311 but before the payment of the Issue Fee. Applicant(s) hereby petition(s) for consideration of this Information Disclosure Statement. Included are: Statement in Accordance with §1.97(e) (attached) and the fee of $180.00 as set forth in §1.17(p).

☐ Copies of each of the references listed on the attached Form PTO-1449 are enclosed herewith.

☐ Copies of references listed on the attached Form PTO-1449 are enclosed herewith EXCEPT THAT:

- ☐ In view of the voluminous nature of references [list as appropriate], and the likelihood that these references are available to the Examiner, copies are not enclosed herewith.
- ☐ If any of the foregoing publications are not available to the Examiner, Applicant will endeavor to supply copies at the Examiner's request.

☒ Copies of only foreign patent documents and non-patent literature are enclosed in accordance with 37 CFR 1.98 (a)(2).

☒ There are no listed references which are not in the English language.

☐ The relevance of those listed references which are not in the English language is as follows:

☒ Attached are copies of search report(s) from corresponding patent application(s), which are listed on the attached Submission Under MPEP 609 D.

☒ Attached are the following non-published pending patent applications and/or nonpatent literature which may be deemed relevant, which are listed on the attached Submission Under MPEP 609 D.

Please charge any deficiency or credit any overpayment to Deposit Account No. 10-0750/PRD2901USNP/HBW.

Respectfully submitted,

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
Phone: (732) 524-2976
Dated: September 17, 2013

By: /Hal Brent Woodrow/
Hal B. Woodrow, Reg. No. 32,501