

07-99050

Clarke, Modet & C^o
COLOMBIA

ESCOBAR - URIBE ASOCIADOS

Intellectual Property

3089/P.

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES**

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-099050- -00001-0000

Ref.: Expediente No. 07-099.050
Solicitud de Patente a nombre de
Janssen Pharmaceutica N.V.

Fecha 2007-10-11 16:42:54 Dep. 2020 NUECREACION
Tra. 2 PATENTES Eve. 1 REGDEPOSITO
Act. 329 CTOINFORMACION Folios: 41

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en la Carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad **Janssen Pharmaceutica N.V.**, domiciliada en Beerse, Bélgica, solicitante de la patente de la referencia, atentamente me permito presentar copia certificada de la solicitud de patente número 11/534,623 presentada en Estados Unidos de América el día 22 de septiembre de 2006, con la debida traducción de lo pertinente.

Señor Superintendente,


JIMENA ESCOBAR URIBE
C.C.39.779.452 de Usaqué
T.P. 68228
Cód. 5376

ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS A QUIENES EL PRESENTE LLEGUE:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos

24 de septiembre de 2007

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con 35 USC 111.

Número de Solicitud: 11/534,623

Fecha de Presentación: 22 de septiembre de 2006

EL CÓDIGO DEL PAÍS Y EL NÚMERO DE SU SOLICITUD DE PRIORIDAD, PARA SER USADA EN LA PRESENTACIÓN EXTRANJERA BAJO EL CONVENIO DE PARÍS ES US11/534,623.

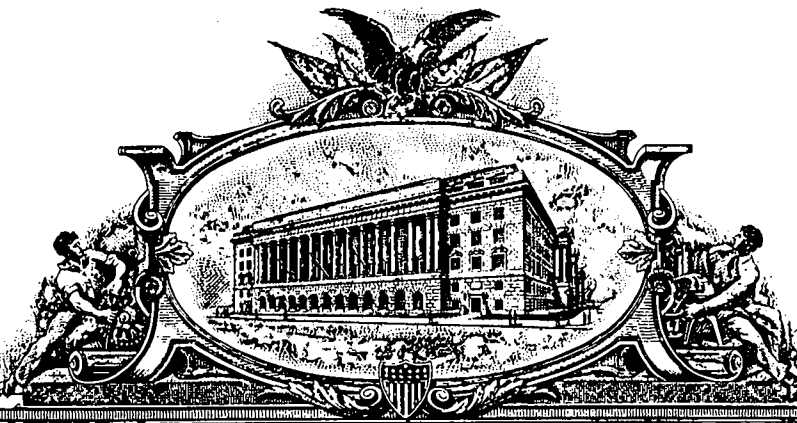
Por la autoridad de
Bajo el Secretario de Comercio para la Propiedad Intelectual y el Director de la Oficina de Patentes y Marcas de los Estados Unidos de América

(fdo) L. EDELEN

Oficial Certificador

Sello oficial de la Oficina de Patentes y Marcas de los Estados Unidos de América

2



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

September 24, 2007

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: *11/534,623*

FILING DATE: *September 22, 2006*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US11/534,623*

By Authority of the

Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office



L. Edelen

L. EDELEN

Certifying Officer

Electronic Acknowledgement Receipt

EFS ID:	1216304
Application Number:	11534623
Confirmation Number:	6277
Title of Invention:	USE OF PALIPERIDONE FOR THE TREATMENT OF A MENTAL DISORDER IN A PSYCHIATRIC PATIENT WITH REDUCED HEPATIC FUNCTION
First Named Inventor:	Sandra Boom
Customer Number:	27777
Filer:	Hal Brent Woodrow
Filer Authorized By:	
Attorney Docket Number:	PRD2583USNP
Receipt Date:	22-SEP-2006
Filing Date:	
Time Stamp:	21:07:02
Application Type:	Utility
International Application Number:	

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	\$1000
RAM confirmation Number	771
Deposit Account	100750
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 and 1.17	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part	Pages
1		PRD2583USNP_PATENT_APPLICATION.pdf	276660	yes	28
	Multipart Description				
	Doc Desc		Start	End	
	Specification		1	23	
	Claims		24	27	
	Abstract		28	28	
Warnings:					
Information:					
2	Transmittal letter	APPLICATION_TRANSMITTAL_PRD2583USNP.pdf	193780	no	1
Warnings:					
Information:					
3	Fee Worksheet (PTO-875)	fee-info.pdf	8410	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			478850		
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. <u>New Applications Under 35 U.S.C. 111</u> 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. <u>National Stage of an International Application under 35 U.S.C. 371</u> 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.					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Boom et al.

For: USE OF PALIPERIDONE FOR THE TREATMENT OF A MENTAL
DISORDER IN A PSYCHIATRIC PATIENT WITH REDUCED HEPATIC
FUNCTION

Date of Deposit: September 22, 2006

Transmittal Letter

The above-identified application is submitted on behalf of following applicants who are believed to be the inventors of the inventions claimed therein:

Sandra Boom
Marie-Henriette Eerdeken

Respectfully submitted,

/Hal Brent Woodrow/
Hal Brent Woodrow, Reg. No. 32,501

**USE OF PALIPERIDONE FOR THE TREATMENT OF A MENTAL
DISORDER IN A PSYCHIATRIC PATIENT WITH REDUCED HEPATIC
FUNCTION**

5 This application claims priority from and benefit of provisional patent applications 60/745,229 filed April 20, 2006 and 60/749,515 filed December 12, 2005, both of which are hereby incorporated by reference herein.

FIELD OF THE INVENTION

10 This invention relates to the use of paliperidone in the treatment of a mental disorder in patients that are hepatically impaired.

BACKGROUND OF THE INVENTION

15 Psychiatric patients often have comorbid conditions that may lead to hepatic impairment. Consequently, to treat these patients with comorbid conditions that potentially cause impaired hepatic function it would be highly desirable to be able to treat these patients for their mental illness with pharmaceuticals that are not to any appreciable degree metabolized in the liver.

20 **SUMMARY OF THE INVENTION**

25 We have discovered that paliperidone, its pharmaceutically acceptable acid addition salts, enantiomeric forms, and esters, are not to any appreciable extent metabolized in the liver. Therefore, these compounds are particularly useful in the treatment of psychiatric patients with impaired liver function.

 In one embodiment, the invention provides for the use of a pharmaceutical composition comprising a therapeutically effective amount of paliperidone, its pharmaceutically acceptable acid addition salts, enantiomeric forms or esters thereof, together with a pharmaceutically acceptable carrier, for the treatment of a mental

disorder in a patient in need thereof, the patient having or at risk of hepatic impairment.

In another embodiment, the invention provides for the use of a pharmaceutical composition comprising a therapeutically effective amount of paliperidone, its
5 pharmaceutically acceptable acid addition salts, enantiomeric forms, or esters thereof, together with a pharmaceutically acceptable carrier, in the manufacture of a medicament for the treatment of a mental disorder in a patient in need thereof, the patient having or at risk of hepatic impairment.

In yet another embodiment, the invention provides a pharmaceutical
10 composition comprising a therapeutically effective amount of paliperidone, its pharmaceutically acceptable acid addition salts, enantiomeric forms, or esters thereof, for the treatment of a mental disorder in a patient in need thereof, the patient having or at risk of hepatic impairment.

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

DETAILED DESCRIPTION

A variety of comorbid conditions which psychiatric patients may present also
20 may lead to hepatic impairment in psychiatric patients such as Wilson's disease, alcoholism, viral hepatitis (e.g. hepatitis B, Hepatitis C adenovirus, Epstein Barr virus, cytomegalovirus and viral haemorrhagic fevers), drug toxicity, hepatocellular carcinoma or metastatic carcinoma, poisoning by various substances, illicit drug use (including Ecstasy and cocaine), Reyes' syndrome, Budd-Chiari syndrome, veno-
25 occlusive disease and autoimmune liver disease. Psychiatric patients that are suspected of hepatic impairment can be identified by examination of their medical records, taking their histories, physical examination or by laboratory testing. Physicians and nurses treating psychiatric patients should be familiar with the symptoms and tests for impaired liver functions. For example patients presenting
30 with symptoms such as jaundice, liver palms, cerebral oedema, etc. should be further

examined for liver impairment. Laboratory tests showing thrombocytopenia, raised bilirubin, low pseudocholinesterase, elevated lactate, raised creatinine etc., should be further investigated. Appropriate techniques to determine whether there is impairment of liver function are known in the art. Normally a battery of tests will be run such as tests for the levels of transaminase (e.g. aspartate aminotransferase, alanine aminotransferase, etc.) and γ -glutamyltransferase, Hepatitis C serologies, Hepatitis B serologies, Hepatitis A serology, Ceruloplasmin, serum protein electrophoresis, hepatic sonogram prothrombin time, CBC with platelet count and serum albumin.

Hepatically impaired patients are those patients that one of ordinary skill in the art, such as a physician, would recognize from testing or diagnosis as having impaired liver function requiring monitoring of their liver condition and/or care being taken in the administration of medication to avoid adverse events (e.g. further damage or failure to properly metabolize and/or clear medicines).

Paliperidone, including its pharmaceutically acceptable acid addition salts, enantiomeric forms, and esters, may be administered for the practice of the present invention. Paliperidone is well known in the art and is described in US Patent 5,158,952 incorporated herein by reference.

As noted in US Patent 5,158,952, paliperidone has basic properties and, consequently, this compound may be converted to its therapeutically active non-toxic acid addition salt forms by treatment with appropriate acids, such as, for example, inorganic acids, such as hydrohalic acid, e.g. hydrochloric, hydrobromic acid and the like, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted into the free base form by treatment with alkali. The term acid addition salt as used

hereinabove also comprises the solvates which such compounds are able to form and said solvates are meant to be included within the scope of the present invention.

Examples of such solvates are e.g., the hydrates, alcoholates and the like.

5 Esters of paliperidone are known in the art and are described in US Patent 5,254,556 incorporated herein by reference. Esters of paliperidone include octanoic acid, decanoic acid, dodecanic acid, tetradecanoic acid or hexadecanoic acid (palmitic acid). The currently preferred ester of paliperidone is paliperidone palmitate.

10 Paliperidone may be formulated with pharmaceutical excipients into a variety of dosage forms as described in US Patent 5,158,952. Paliperidone will in one embodiment of the present invention be provided in an oral dosage form. Suitable oral dosage forms include but are not limited to tablets, pills, fast dissolving dosage forms, controlled release or extended release dosage forms. Currently preferred are extended release OROS oral dosage forms which are well known in the art. Examples of oral dosage forms of paliperidone are described in US 20040092534, US 15 20050208132 and US 20050232995, all hereby incorporated by reference herein. Paliperidone palmitate, including its pharmaceutically acceptable acid addition salts, and stereoisomeric forms, is also well known in the art and may also be formulated with pharmaceutical excipients into a variety of dosage forms as described in US Patent 5,254,556. Currently, it is preferred to administer paliperidone palmitate in a 20 depot.

25 Paliperidone palmitate is considered to be a potentially valuable prodrug of paliperidone. A pharmaceutical composition suitable as an injectable solution of paliperidone palmitate may comprise a formulation of paliperidone palmitate in an appropriate oil for prolonged action; for example, peanut oil, sesame oil, cottonseed oil, corn oil, soy bean oil, synthetic glycerol esters of long chain fatty acids and mixtures of these and other oils.

30 In another embodiment, a pharmaceutical composition suitable as an efficient, well-tolerated, sustained or delayed release (depot) formulation for administration of paliperidone palmitate by intramuscular or subcutaneous injection may comprise a suspension of paliperidone palmitate in aqueous solution. Ideally, suitable aqueous

depot formulations 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:

- 5 (a) from 3 to 20% (w/v) of the prodrug;
- (b) from 0.05 to 2% (w/v) of a wetting agent;
- (c) one or more buffering agents;
- (d) from 0.5 to 2% (w/v) of a suspending agent;
- (e) up to 2% (w/v) preservatives; and
- 10 (f) water q.s. ad 100%.

In yet another embodiment, the above composition may comprise a dispersion of particles consisting essentially of a therapeutically effective amount of crystalline paliperidone palmitate having a surfactant absorbed to the surface thereof in an amount effective in maintaining a specific surface area $>4 \text{ m}^2/\text{g}$ (corresponding to an effective average particle size of less than 2,000 nm), in a pharmaceutically acceptable carrier comprising water. Preferably, the specific surface area is $>6 \text{ m}^2/\text{g}$, and in particular is in the range from 10 to $16 \text{ m}^2/\text{g}$. Useful surface modifiers are believed to include those which physically adhere to the surface of the paliperidone palmitate 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. 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.

Suitable aqueous depot formulations are well known in the art and specific details are provided in US Patent 6,077,843, US Patent 6,320,048 and US Patent 6,555,544, which are all incorporated by reference herein. Typically, suitable aqueous depot formulations will be administered approximately every three weeks or even at longer intervals where possible. The dosage should range from about 2 to 4 mg/kg body weight.

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 the term “mental disorder” also encompasses mental illnesses and refers 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, its salts, enantiomers and esters 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 conditions 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),
5 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),
10 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
15 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
20 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
25 (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
30 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),

5 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),

10 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

15 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,

20 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),

25 Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

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,

30 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 would be from about 0.01mg/kg to about 2 mg/kg body weight. In one embodiment of present invention wherein
 5 paliperidone is orally administered a dosage form to a subject once a day is preferred. The mg of compound delivered in such a dosage form to the patient may be from 0.25 to about 20 mg (e.g. 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, and 20 mg) per oral dosage form.

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

EXAMPLE 1

15
Objectives: to investigate the metabolic pathways of paliperidone and excretion of paliperidone and its metabolites in healthy adult male subjects, both CYP2D6 poor and extensive metabolizers, after administration of a single 1-mg oral dose of ¹⁴C-paliperidone. In addition, to evaluate the safety and tolerability of paliperidone, as
 20 well as the relationship between genotypes (CYP2D6, CYP3A4, CYP3A5, UGT1A1, and UGT1A6) and exposure to paliperidone and its metabolites.

Methodology: Single-center, single-dose open-label study of the absorption, metabolism, and excretion (AME) of paliperidone in healthy men (3 extensive and 3
 25 poor metabolizers based on CPY2D6 phenotype). Eligible subjects were admitted to the study center the evening before study drug administration and remained at the study center until 168 hours after dosing (or longer if required up to a maximum of 14 days). Each subject received a single oral dose of ¹⁴C-paliperidone with total
 30 radioactivity below 10000 μSv (16 μCi). Blood samples for plasma pharmacokinetic

16

profile were obtained immediately before study drug administration and 0.5, 1, 1.5, 3, 6, 12, 16, 36, 48, 72, 96, 120, 144 and 168 hours postdose. Blood samples were obtained 2, 4, 8, and 24 hours postdose for determination of ^{14}C in whole blood.

Samples for determination of serum creatinine were obtained 2, 4, 8, and 24 hours

5 postdose. Urine was collected immediately prior to drug administration and from 0-4, 4-8, 8-12, 12-16, 16-24, 24-36, 36-48, 48-72, 96-120, 120-144, and 144-168 hours after study drug administration. Fecal samples were collected per each stool, once before study drug administration and in the period from 0-168 hours after study drug administration. Collections of urine and feces (per 24 hours) were to continue beyond
10 168 hours, to a maximum of 336 hours (Day 15) for subjects who excrete radioactivity slowly (2 latest 24-hour urine collections each $\geq 2\%$ of total radioactive dose) or have <7 feces stool samples over the 0 to 168-hour period. ^{14}C radioactivity was measured in plasma, urine, and feces. Aliquots of the 0- through 24-hour urine collections were analyzed for creatinine. Plasma concentrations of paliperidone and
15 risperidone were determined by means of a validated LC-MS/MS method. The ^{14}C -labeled moiety in plasma and urine was determined by liquid scintillation counting. For all plasma samples, the lower limits of quantification for paliperidone and risperidone were 0.100 ng/mL. For all plasma and urine samples the lower limits of quantification for ^{14}C -paliperidone was 72 dpm/mL ($=2.0\text{ ng-eq/mL}$).

20

Number of Subjects (planned and analyzed): Six healthy men, 3 extensive and 3 poor metabolizers based on CYP2D6 phenotype were to participate in the study. Five subjects, 3 extensive and 2 poor metabolizers, received a single dose of ^{14}C -paliperidone, completed the study (i.e., completed all assessments through Day 8) and
25 were considered valuable for safety (the Safety Analysis Set), as well as for pharmacokinetics.

Diagnosis and Main Criteria for Inclusion: Subjects were healthy white males between the ages of 40 and 60 years. Subjects were healthy based on medical history,
30 physical examination, clinical laboratory evaluate, and electrocardiogram.

17

PRD2583USNP

Dextromethorphan metabolic ratio of >0.345 (poor metabolizer) or <0.0255 (extensive metabolizer). Body Mass Index (MBI): (weight [kg]/height [m^2]) between 20 and 28 kg/m^2 , inclusive.

- 5 **Test Product, Dose and Mode of Administration Batch No.:** Single oral 0.988-mg dose of ^{14}C -paliperidone, oral solution (aqueous formulation at a final concentration of 0.0984 mg/mL). Batch No.: unlabeled paliperidone oral solution: ZR076477EIA031 (manufacturing date: 23 April 2003, retest date: 23 October 2004): ^{14}C -paliperidone: 1763 (expiration date: not applicable)

10

- Criteria for Evaluation:** Pharmacokinetics: Plasma paliperidone. ^{14}C radioactivity and metabolite profiles were determined. Plasma C_{max} , t_{max} , AUC_{last} , AUC_{24} , AUC_{∞} , λ_Z , $t_{1/2term}$, CL/F of ^{14}C and paliperidone were estimated by non-compartmental analysis. Based on the individual urine excretion data and on the serum creatinine concentrations, A_e , A_e , % dose, CL_R , $CL_{R,24h}$ and CL_{er} and paliperidone and CL_{GFR} , and CL_{act} of paliperidone were estimated. The excretion half-life of ^{14}C in urine was also estimated based on excretion rate-time profiles.

15

- Safety:** Evaluation was based on the incidence, type, and severity of all treatment-emergent adverse events, and on change from screening to the end of the study in clinical laboratory results, vital sign measurements, and postural changes in blood pressure and heart rate.

20

- Statistical Methods:** Pharmacokinetics: Plasma concentrations of ^{14}C and paliperidone as well as estimates for pharmacokinetic parameters were listed and graphically presented, and the excretion analysis of total radioactivity in plasma, urine and feces were summarized. Descriptive statistics were calculated, including summaries by CYP2D6 phenotype.

25

PRD2583USNP

Safety: The number of subjects with adverse events was summarized. Summary statistics were calculated for clinical laboratory values. Other safety data were listed by individual sect. Changes in blood pressure and heart rate measurements were also presented graphically.

5

Summary-Conclusion

10 Demographic and baseline characteristics: Five white men, 3 extensive metabolizers and 2 poor metabolizers, received study medication and completed the study. The ages ranged from 40 to 63 years (mean: 51.2 year), the body weights ranged from 68.7 to 78.6 kg (mean: 73.38 kg), and BMI ranged from 24 to 28 kg/m² (mean: 25.5 kg/m²).

15

Pharmacokinetic Results:

Pharmacokinetics of Total Radioactivity (TR) and paliperidone (UD) in plasma;

The mean (SD) pharmacokinetic parameters of TR and UD after administration of a
20 single oral dose of ¹⁴C-paliperidone are summarized in Table A.

Table A: Plasma Pharmacokinetic Parameters of ^{14}C -Labeled Moiety and Unchanged Paliperidone (Mean $\pm$ SD) After a Single Dose of 1-mg ^{14}C -Paliperidone

5

	ALL (N=5)	EM(N=3)	PM (N=2)
^{14}C-Labeled Moiety (TR)			
$C_{\max}$, ng-equivalent/mL	9.54 $\pm$ 1.35	9.40 $\pm$ 1.73	9.75 $\pm$ 1.06
$t_{\max}$, h	1.40 $\pm$ 0.224	1.50 $\pm$ 0.00	1.25 $\pm$ 0.354
AUC_{24} , ng-eq·h/mL	114 $\pm$ 19.9	116 $\pm$ 27.3	112 $\pm$ 7.8
AUC_{24} , ng-eq·h/mL	175 $\pm$ 30.7	179 $\pm$ 41.9	168 $\pm$ 9.90
$t_{1/2\text{term}}$, h	15.2 $\pm$ 2.15	15.4 $\pm$ 1.35	14.9 $\pm$ 3.82
CL/F, mL/min	97.9 $\pm$ 17.6	96.8 $\pm$ 24.4	99.6 $\pm$ 6.22
Unchanged Paliperidone (UD)			
$C_{\max}$ ng/mL	8.85 $\pm$ 1.31	8.59 $\pm$ 1.79	9.24 $\pm$ 0.00707
$t_{\max}$, h	1.30 $\pm$ 0.274	1.33 $\pm$ 0.289	1.25 $\pm$ 0.354
AUC_{24} , ng·h/mL	111 $\pm$ 22.0	113 $\pm$ 30.1	109 $\pm$ 9.90
AUC_{∞} ng·h/mL	187 $\pm$ 29.3	190 $\pm$ 38.4	182 $\pm$ 19.8
$t_{1/2\text{term}}$, h	24.8 $\pm$ 4.35	24.1 $\pm$ 4.49	26.0 $\pm$ 5.59
CL/F, mL/min	91.0 $\pm$ 15.0	90.3 $\pm$ 20.0	92.1 $\pm$ 10.0
Ratio AUC_{24} : UD/TR	0.970 $\pm$ 0.0250	0.965 $\pm$ 0.0311	0.977 $\pm$ 0.0205
EM: extensive metabolizer; PM: poor metabolizer			

In the overall population, average peak plasma concentration of TR (9.54 ng-eq/mL) was attained 1.40 hours after dosing. Average peak plasma concentration of UD (8.85 ng/mL) was reached after 1.30 hours. The terminal half-life of TR and UD was on average 15.2 hours and 24.9 hours, respectively, This difference was probably caused by a higher LLOQ for TR compared to UD, AUC_{∞} values of TR averaged 175 ng-eq.h/mL, those of UD were 187 ng.h/mL. At 24 hours after dosing the percentage of UD versus TR in plasma is on average 97.0%. No differences are found between CYP2D6 extensive and poor metabolizers.

Excretion in Urine and Feces:

At 7 days after a single oral dose of ^{14}C -paliperidone, 91% of the administered radioactivity has been excreted as ^{14}C -labeled moiety. The cumulative excretion of the TR amounted to 80% in the urine (Table B) and 11% in the feces. There were no differences between extensive and poor metabolizers in urinary excretion (% of the dose) of ^{14}C -labeled moiety. Furthermore no discrimination could be made between extensive (13%) and poor (8%) metabolizers of excretion of ^{14}C labeled moiety in feces.

Table B: Clearance and Urine Parameters of ^{14}C -Labeled Moiety (Mean $\pm$ SD)
After Single Dose of 1-mg ^{14}C Paliperidone

	All (N=5)	EM (N=3)	PM (N=2)
^{14}C-Labeled Moiety			
Ae, % dose	79.6 $\pm$ 4.20	77.6 $\pm$ 0.775	82.7 $\pm$ 6.15
CL _R , mL/min	76.8 $\pm$ 13.6	74.1 $\pm$ 18.5	80.8 $\pm$ 1.20
CL _{CR} , mL/min	113 $\pm$ 10.3	108 $\pm$ 7.37	121 $\pm$ 10.5
Unchanged Paliperidone			
Ae, % dose	59.4 $\pm$ 7.12	55.7 $\pm$ 6.66	64.9 $\pm$ 3.68
CL _R , mL/min	53.1 $\pm$ 9.47	49.2 $\pm$ 8.59	59.1 $\pm$ 9.69

Safety Results:

Two of the 5 subjects who received study education experienced treatment-emergent adverse events: moderately severe postural hypotension and syncope in 1 subject and mild allergic reaction (described as infraorbital swelling probably due to an allergic reaction, and considered doubtfully related to the study medication) and asthenia in the second subject. With the exception of allergic reaction which was persisting at the end of the study, the adverse events resolved without treatment intervention. There

PRD2583USNP

were no deaths, no serious adverse events, and no subject discontinued from the study due to an adverse event.

There were no clinically relevant changes in laboratory test results. With the exception of postural hypotension which was reported as an adverse event in 1 subject, there were no clinically relevant changes in vital sign measurements.

Conclusion:

The unchanged drug paliperidone accounted for a large part of the total radioactivity in plasma. The percentage of UD versus TR in plasma is on average 97%. There were no differences in paliperidone pharmacokinetic parameters observed between CYP2D6 extensive and poor metabolizers. No effect of genotype was observed for CYP2D6, UGT1A1 or UGT1A6 on the plasma exposure of TR and UD.

Seven days after administration of a single oral dose of 1 mg ¹⁴C-paliperidone to 5 healthy male subjects, 91% of the dose was excreted in urine and feces as ¹⁴C-labeled moiety. The cumulative excretion of the TR amounted to 80% in the urine and 11% in the feces. The cumulative urinary excretion of unchanged paliperidone amounted to 59%. About 50% of the UD is excreted by means of filtration; the other half of UD is cleared renally by active processes.

The administration of a single oral 1-mg dose of ¹⁴C-paliperidone as a normal solution was safe and well tolerated in healthy men.

EXAMPLE 2

Objectives: The primary objective of this study was to investigate the single-dose pharmacokinetics of immediate-release (IR) paliperidone, after oral administration, in

22

subjects having moderate hepatic impairment (“hepatically-impaired subjects”) compared with subjects having normal hepatic function (“healthy subjects”). The secondary objective was to document the plasma protein binding and disposition of the enantiomers of paliperidone. In addition, the tolerability and safety profile of IR paliperidone was compared between hepatically impaired subjects and healthy subjects.

Methodology: This was a single-dose, parallel-group, open-label, single-center, Phase I study of IR paliperidone in subjects having either normal or moderately impaired hepatic function. The groups, consisting of 10 subjects each, were demographically matched with respect to age, weight, sex, and ethnicity. The study consisted of a screening period of up to 3 weeks and an open-label, single-dose treatment period (Days 1 through 5). On Day 1, a single dose of 1 mg IR paliperidone oral solution was administered after a fast of at least 10 hours; subjects continued to fast for 4 hours following study drug administration. The 96-hour follow-up consisted of serial sample collection of blood and urine for pharmacokinetic analysis and safety and tolerability assessments. Subjects remained confined to the study site through the 72-hour pharmacokinetics sampling, and consumed standard institutional meals while in the study site. Subjects were released after the 72-hour sampling, then returned to the study site on Day 5 before the 96-hour pharmacokinetics sampling; end-of-study procedures were performed immediately hereafter. A blood sample for DNA isolation was collected to allow for genetic analysis as necessary.

Number of Subjects (planned and analyzed): Ten subjects were planned for each hepatic function group; 10 subjects in each group completed the study and were analyzed for pharmacokinetics and safety.

Diagnosis and Main Criteria for Inclusion: The study was conducted in men and women, aged 18 through 75 years, inclusive. One group of subjects had moderate hepatic impairment, with stable hepatic disease, a total Child-Pugh score of between 7

PRD2583USNP

and 9, inclusive, and blood pressure that was controlled and stable on antihypertensive agents; the other group had normal hepatic function.

Test Product, Dose and Mode of Administration, Batch No: 1 mg IR paliperidone
5 (R076477) oral solution; batch 04C29/F044.

Duration of Treatment: This was a single-dose study.

Criteria for Evaluation: Pharmacokinetics: Plasma and urine concentrations of the
10 paliperidone enantiomers (+) R078543 and (-) R078544 were determined using an
LC-MS/MS method. Concentrations of paliperidone were calculated as the sum of
the enantiomer concentrations. In addition, serum and urine concentrations of
creatinine were determined for the calculation of CL_{CR} . The protein binding and
unbound fraction was determined for the 2 paliperidone enantiomers. The unbound
15 fraction for paliperidone was calculated.

Based on the actual pharmacokinetic blood sampling times and actual urine collection periods, the following plasma and urine pharmacokinetic parameters were determined for paliperidone and its enantiomers: C_{max} , t_{max} , t_{last} , AUC_{last} , λ_Z , $t_{1/2}$, AUC_{∞} ,
20 $\%AUC_{\infty,ex}$, CL/F , AUC_{∞} +/- ratio, C_t +/- ratio per time point, unbound AUC_{∞} ,
unbound CL/F or unbound CL (if relevant), A_e (per collection interval and overall),
 $A_e, \%dose$, $Excr. Rate$, Vd_2 , CR_R , CL_{GFR} , CL_{act} , CL_{act}/CL_R , $CL_{act}/(CL/F)$, CL_{CR} , and
 CL_{NR} .

25 **Safety:** Adverse events, clinical laboratory tests, including prolactin, vital sign measurements, physical examinations, and 12-lead electrocardiograms (ECGs) were analyzed to assess safety.

Statistical Methods:

30

24

PRD2583USNP

Pharmacokinetics: Descriptive statistics were evaluated for the plasma concentrations at each sampling time, and for all pharmacokinetic parameters of paliperidone and its enantiomers for each hepatic function group. Graphical exploration of the paliperidone and enantiomer plasma concentrations and urine data, and the derived pharmacokinetic parameters, was performed. In addition, the enantiomer disposition was compared between the groups.

Log-transformed PK parameters were fit to a general linear model with hepatic function group as fixed effect.

Safety: All subjects were analyzed; statistical analyses were descriptive [? Does info need to be added here?].

Summary-Conclusions

Pharmacokinetic Results: The fraction of unbound paliperidone in plasma was higher in hepatically-impaired subjects compared with healthy subjects and averaged 0.353 and 0.279 respectively. The difference in plasma protein binding between the groups most likely results from the reduced α_1 -acid glycoprotein (α_1 -AGP) plasma concentration in hepatically-impaired subjects, since the fraction of unbound drug appears to be inversely related to the α_1 -AGP plasma concentration.

25

Predose Plasma Concentration of Albumin, α_1 -AGP, and Total Protein and Unbound Fraction for Paliperidone, (+)R078543, and (-)R078544

		Healthy Subjects (n=10)	Hepatically-Impaired Subjects (n=10)
5	-----		
10	Albumin (g/dL)	4.3 $\pm$ 0.2	3.3 $\pm$ 0.6
	A ₁ -AGP (mg/dL)	77.0 $\pm$ 18.8	46.6 $\pm$ 17.1
	Total Protein (g/dL)	7.2 $\pm$ 0.2	6.9 $\pm$ 0.7
	Unbound Fraction		
	(+) R078543	0.215 $\pm$ 0.0469	0.306 $\pm$ 0.0687
15	Unbound Fraction		
	(-) R078544	0.385 $\pm$ 0.0416	0.457 $\pm$ 0.0504
	Unbound Fraction		
	Paliperidone	0.279 $\pm$ 0.0492	0.353 $\pm$ 0.0564 ^a

All values are mean (SD).

^aDescriptive statistics based on n=8, excluding Subjects 0005 and 0006.

Overall, hepatically-impaired subjects achieved lower total plasma concentrations than healthy subjects. AUC and C_{max} values of paliperidone and each of its enantiomers were lower for hepatically-impaired subjects than for healthy subjects: in each case, C_{max} was approximately 35% lower and AUC_∞ approximately 27% lower. After correction for unbound fraction, the exposure was comparable between the groups. The median time to reach maximum plasma concentration was around 1 hour for both groups, although somewhat more variable among the hepatically-impaired subjects.

Paliperidone plasma concentration declined with a mean terminal half-life of 23.6 hours for healthy subjects and 26.5 hours for hepatically-impaired subjects.

The CL/F for paliperidone was about 35% higher in hepatically-impaired subjects compared with healthy subjects which is consistent with the lower AUC_∞. Moreover, hepatically-impaired subjects had 47% higher volumes of distribution for total

26

Paliperidone compared with healthy subjects. Based on unbound concentrations, however, the clearance and volume of distribution were comparable between the groups.

- 5 Hepatically-impaired subjects showed more variable renal excretion profiles (i.e. larger %CV) than healthy subjects. There were no other apparent differences in urinary excretions parameters between the hepatic function groups. Approximately 50% of the dose was excreted unchanged into urine and did not differ between the groups. Renal clearance was not much different between the groups (67.4 vs. 51.2
- 10 ng/ml), which can be expected because the unbound plasma concentrations between the groups are comparable. Renal function, as determined by the creatinine clearance, was almost identical between the groups. Active renal clearance accounted on average for approximately 45% of the renal clearance in both groups.

Paliperidone								
Healthy Subjects					Hepatically-Impaired Subjects			
	n	Total	n	Unbound	n	Total	n	Unbound
C _{max} ,ng/mL	10	7.14 ± 2.28	10	1.81 ± 0.292	10	4.57 ± 1.05	10	1.59 ± 0.318
AUC _∞ , ng.h/ml	10	176 ± 64.4	10	45.8 ± 8.72	9	128 ± 42.5	8	45.7 ± 12.6
t _{max} , h	10	1.00 (1.00 -2.00)	10	1.25 (1.00-2.00)	10	1.25 (0.25 - 4.00)	10	1.25 (0.25 - 4.00)
t _{1/2} , h	10	23.6 ± 3.6		ND	10	26.5 ± 6.4		ND
CL/F, ml/min	10	106 ± 34.9	10	370 ± 67.1	9	143 ± 43.4	8	386 ± 99.3
V _d , L	10	211 ± 59.6	10	748 ± 144	9	311 ± 65.2	8	857 ± 146
CL _R , ml/min	10	51.2 ± 13.4		ND	9	67.4 ± 34.0		ND
CL _{NR} , ml/min	10	54.4 ± 23.7	10	188 ± 56.8	9	75.1 ± 16.2	8	205 ± 30.7
Ae,%dose	10	50.1 ± 7.94		ND	10	44.7 ± 10.62		ND
Mean ± SD; for t _{max} : median (range); ND: Not determined.								

Mean ± SD; for t_{max}, median (range); ND: Not determined.

- 15 When the data from the two hepatic function groups were pooled, there was no apparent relationship between clearance of paliperidone or its enantiomers and most measures of hepatic function (i.e. albumin and bilirubin concentrations, prothrombin time, and Child-Pugh score); there was an inverse relationship between clearance of
- 20 paliperidone or its separate enantiomers and α₁-AGP concentration.

Exposure to both enantiomers was higher in healthy subjects compared with hepatically-impaired subjects; furthermore, in both groups, exposure to (+) R078543 was high than exposure to R078544. The (+)/(-) ration based on the AUC for the total

plasma concentrations was somewhat larger in healthy subjects compared with hepatically-impaired subjects (i.e. 1.67 and 1.38 respectively). Based on unbound concentrations, however, the exposure to both enantiomers was within the same range, and the (+)/(-) AUC ration was comparable between healthy and hepatically-impaired subjects (i.e., 0.914 and 0.886, respectively).

Safety Results: The only adverse events that were reported in more than 1 subject in either group were hyperprolactinemia (see below) and dizziness (in 2 hepatically-impaired subjects only). Treatment-emergent increase in hepatic enzymes were noted in 1 hepatically-impaired and 1 healthy subject. These elevations were only slightly above the baseline value in the hepatically-impaired subject and less than twice the upper limit of normal in the healthy subject, and thus were not considered clinically important.

An increase in prolactin from the mean predose levels was seen in both hepatically-impaired and healthy subjects at 36 hours; thereafter mean levels decreased. Because the investigator was unblinded to the laboratory results, increases in prolactin levels were reported as adverse events in 8 hepatically-impaired and 6 healthy subjects; these adverse events were considered mild and very likely related to study drug by the investigator.

There were no unexpected findings in vital signs; no subject in either group met the criteria for orthostatic hypotension. Furthermore, no subjects had clinically important abnormal ECG values (including QT values).

Conclusion:

PRD2583USNP

After oral administration of 1 mg paliperidone IR, hepatically impaired subjects had a lower mean $C_{\max}$ ($\approx 35\%$) and AUC_{∞} ($\approx 27\%$) for total paliperidone and its enantiomers than did healthy subjects.

- 5 The protein binding differed between the hepatic function groups. The unbound fraction of paliperidone was approximately 27% higher in hepatically-impaired subjects. Taking this difference in protein binding into account $C_{\max}$ and AUC_{∞} for the unbound fraction of paliperidone were comparable across the hepatic function groups. $C_{\max}$ was approximately 12% lower, and AUC_{∞} approximately 5% lower, in
10 hepatically-impaired subjects compared with healthy subjects.

The mean terminal half-life for IR paliperidone and its enantiomers was between 23.6 and 25.0 hours for healthy subjects, and between 26.5 and 27.5 hours for hepatically-impaired subjects.

- 15 Paliperidone IR, 1 mg, was tolerated equally well by healthy and hepatically-impaired subjects.

NOVEDAD DE LA INVENCION

REIVINDICACIONES

5 1.- Un método para el tratamiento de pacientes psiquiátricos que tienen o que están en riesgo de deterioro hepático, que comprende administrar una cantidad terapéuticamente efectiva de paliperidona, sus sales ácidas de adición farmacéuticamente aceptables, formas enantioméricas y ésteres de la misma a dicho paciente psiquiátrico en necesidad del mismo.

10 2.- El método de conformidad con la reivindicación 1, caracterizado además porque el paciente psiquiátrico está en necesidad de tratamiento para psicosis.

 3.- El método de conformidad con la reivindicación 2, caracterizado además porque el paciente psiquiátrico está en necesidad de
15 tratamiento para esquizofrenia.

 4.- El método de conformidad con la reivindicación 2, caracterizado además porque el paciente psiquiátrico está en necesidad de tratamiento para trastorno bipolar.

 5.- El método de conformidad con la reivindicación 1,
20 caracterizado además porque el paciente psiquiátrico está en necesidad de tratamiento para un trastorno mental seleccionado del grupo que consiste en Retraso Mental Leve (317), Retraso Mental Moderado (318.0), Retraso Mental Severo (318.1), Retraso Mental Profundo (318.2) Retraso Mental con

Severidad no Especificada (319), Trastornos Autistas (299.0) Trastorno de Rett (299.80), Trastornos Desintegradores Infantiles (299.10), Trastornos de Asperger (299.80), Trastorno Generalizado del Desarrollo no Especificado de Otra forma (299.80), Trastorno de Déficit de Atención/Hiperactividad de Tipo

5 Combinado (314.01), Trastorno de Déficit de Atención/Hiperactividad de Tipo Predominantemente no Atento (314.00), Trastorno de Déficit de Atención/Hiperactividad de Tipo Predominantemente Hiperactivo-Impulsivo (314.01), Trastorno de Déficit de Atención/Hiperactividad NOS (314.9), Trastorno de Conducta (de Tipo al Inicio de la Infancia y en la Adolescencia

10 312.8), Trastorno de Oposición Desafiante (313.81), Trastorno de Comportamiento Perturbado no Especificado de otra forma (312.9), Tipo Agresivo Solitario (312.00), Trastorno de Conducta, Tipo No Diferenciado (312.90), Trastorno de Tourette (307.23), Trastorno Motriz Crónico o Vocal (307.22), trastorno de Tic Transitorio (307.21), Trastorno de Tic NOS (307.20),

15 Delirio por Intoxicación con Alcohol (291.0), Delirio por Abstinencia de Alcohol (291.0), Demencia Persistente Inducida por Alcohol (291.2), Trastorno Psicótico Inducido por Alcohol con Delusiones (291.5), Trastorno Psicótico Inducido por Alcohol con Alucinaciones (291.3), Intoxicación por Anfetamina o un Simpatomimético de Acción Similar (292.89), delirio por anfetaminas o

20 simpatomiméticos de acción similar (292.81), trastorno psicótico por anfetamina o inducido por simpatomimético de acción similar con delusión (292.11), trastorno psicótico por anfetamina o inducido por simpatomimético de acción similar con alucinaciones (292.12), trastorno psicótico inducido por

cannabis con delusiones (292.11), trastorno psicótico inducido por cannabis con alucinaciones (292.12), intoxicación por cocaína (292.89), delirio por intoxicación con cocaína (292.81), trastorno psicótico inducido por cocaína con delusiones (292.11), trastornos psicótico inducido por cocaína con alucinaciones (292.12), intoxicación con alucinógenos (292.89), delirio por intoxicación con alucinógenos (292.81), trastorno psicótico inducido por alucinógenos con delusiones (292.11), trastorno psicótico inducido por alucinógeno con delusiones (292.12), trastorno de humor inducido por alucinógenos (292.84), trastorno de ansiedad inducido por alucinógenos (292.89), trastorno relacionado con alucinógenos no especificado de otra forma (292.9), intoxicación por inhalantes (292.89), delirio por intoxicación con inhalantes (292.81), demencia persistente inducida por inhalantes (292.82), trastorno psicótico inducido por inhalantes con delusiones (292.11), trastorno psicótico inducido por inhalantes con alucinaciones (292.12), trastorno de humor inducido por inhalantes (292.89), trastorno de ansiedad inducido por inhalantes (292.89), trastorno relacionado con inhalantes no especificado de otra forma (292.9), delirio por intoxicación con opioides (292.81), trastorno psicótico inducido por opioides con delusiones (292.11), delirio por intoxicación con opioide (292.81), trastorno psicótico inducido por opioides con alucinaciones (292.12), trastorno de humor inducido por opioides (292.84), intoxicación por fenciclidina (PCP) o arilciclohexilamina de acción similar (292.89), delirio por intoxicación con fenciclidina (PCP) o arilciclohexilamina de acción similar (292.81), trastorno psicótico inducido por fenciclidina (PCP) o

arilciclohexilamina de acción similar con delusiones (292.11), trastorno
 psicótico inducido por fenciclidina (PCP) o arilciclohexilamina de acción similar
 con alucinaciones (292.12), trastorno de humor por fenciclidina (PCP) o
 arilciclohexilamina con acción similar (292.84), trastorno de ansiedad inducido
 5 por fenciclidina (PCP) o arilciclohexilamina de acción similar (292.89),
 trastorno relacionado con fenciclidina (PCP) o arilciclohexilamina de acción
 similar no especificada de otra forma (292.9), intoxicación por sedante,
 hipnótico u ansiolítico (292.89), delirio por intoxicación con sedante, hipnótico
 o ansiolítico (292.81), delirio por abstinencia de sedante, hipnótico o ansiolítico
 10 (292.81), demencia persistente inducida por sedante, hipnótico o ansiolítico
 (292.82), trastorno psicótico inducido por sedante, hipnótico o ansiolítico con
 delusiones (292.11), trastorno psicótico inducido por sedante hipnótico o
 ansiolítico con alucinaciones (292.12), trastorno de humor inducido por
 sedante, hipnótico o ansiolítico (292.84), trastorno de ansiedad inducido por
 15 sedante, hipnótico o ansiolítico (292.89), intoxicación por otras sustancias (o
 desconocidas) (292.89), delirio inducido por otras sustancias (o desconocidas)
 (292.81), demencia persistente inducida por otras sustancias (o desconocidas)
 (292.82), trastorno psicótico inducido por otras sustancias (o desconocidas)
 con delusiones (292.11), trastorno psicótico inducido por otras sustancias (o
 20 desconocidas) con alucinaciones (292.12), trastorno de humor inducido por
 otras sustancias (o desconocidas) (292.84), trastorno de ansiedad inducido
 por otras sustancias (o desconocidas) (292.89), trastorno por otras sustancias
 (o desconocidas) no especificadas de otra forma (292.9), trastorno obsesivo

compulsivo (300.3), trastorno de estrés postraumático (309.81), trastorno de ansiedad generalizado (300.02), trastorno de ansiedad no especificado de otra forma (300.00), trastorno dismórfico del cuerpo (300.7), hipocondriasis (o neurosis hipocondríaca) (300.7), trastorno de somatización (300.81), trastorno somatoforme no diferenciado (300.81), trastorno somatoforme no especificado de otra forma (300.81), trastorno explosivo intermitente (312.34), cleptomanía (312.32), apuesta patológica (312.31), piromanía (312.33), tricotilomanía (312.39), y trastorno de control por impulso NOS (312.30), esquizofrenia, tipo paranoide (295.30), esquizofrenia desorganizada (295.10), esquizofrenia tipo catatónica (295.20), esquizofrenia tipo indiferenciado (295.90), esquizofrenia de tipo residual (295.60), trastorno esquizofreniforme (295.40), trastorno esquizoafectivo (295.70), trastorno de delusión (297.1), trastorno psicótico breve (298.8), trastorno psicótico compartido (297.3), trastorno psicótico debido a una condición médica general con delusiones (293.81), trastorno psicótico debido a una condición médica general con alucinaciones (293.82), trastorno psicótico no especificado de otra forma (298.9), depresión mayor, episodio único, severo sin características psicóticas (296.23), depresión mayor, recurrente, severa sin características psicóticas (296.33), trastorno bipolar, mixto, severo, sin características psicóticas (296.63), trastorno bipolar, mixto, severo, con características psicóticas (296.64), trastorno bipolar, maniaco, severo, sin características psicóticas (296.43), trastorno bipolar, maniaco, severo, con características psicóticas (296.44), trastorno bipolar depresivo, severo, sin características psicóticas (296.53), trastorno bipolar,

depresivo, severo, con características psicóticas (296.54), trastorno bipolar II (296.89), trastorno bipolar no especificado de otra forma (296.80), trastornos de personalidad, paranoide (301.0), trastornos de personalidad, esquizoideos (301.20), trastorno de personalidad, esquizotípicos (301.22), trastornos de personalidad, antisociales (301.07), y trastornos de personalidad, limítrofes (301.83).

WE CLAIM:

1. A method for the treatment of psychiatric patients having or at risk of hepatic
5 impairment comprising administering a therapeutically effective amount of
paliperidone its pharmaceutically acceptable acid addition salts, enantiomeric forms
and esters thereof to such psychiatric patient in need thereof.
2. The method of claim 1 wherein the psychiatric patient is in need of treatment for
10 psychosis.
3. The method of claim 2 wherein the psychiatric patient is in need of treatment for
schizophrenia.
- 15 4. The method of claim 2 wherein the psychiatric patient is in need of treatment for
bipolar disorder.
5. The method of claim 1 wherein the psychiatric patient is in need of treatment for a
mental disorder selected from the group consisting of Mild Mental Retardation (317),
20 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
25 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
30 (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
5 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
10 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
15 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
20 (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
25 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
30 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
- 5 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
- 10 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
- 15 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),
- 20 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),
- 25 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
- 30 (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70),

PRD2583USNP

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
5 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
10 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
15 (301.7), and Personality Disorders, Borderline (301.83).



Abstract of the Invention

- The present invention provides a method for the treatment of psychiatric patients
- 5 having or at risk of hepatic impairment comprising administering a therapeutically effective amount of paliperidone, its pharmaceutically acceptable acid addition salts, enantiomeric forms and esters thereof to psychiatric patients in need thereof.