METHOD FOR TREATING BIPOLAR DISORDER

This invention provides a method for using 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine, (hereinafter referred as "olanzapine"), for the treatment of bipolar disorder.

Bipolar Disorder is a psychiatric condition which is prevelant across cultures and age groups. The lifetime prevalence of Bipolar Disorder can be as high as 1.6%. DSM-IV, p. 353 (American Psychiatric Association, Washington, D.C. 1994). Bipolar Disorder is a recurrent disorder characterized by one or more Manic Episodes immediately before or after a Major Depressive Episode or may be characterized by one or more Major Depressive Episodes accompanied by at least one Hypomanic Episode. Additionally, the symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. In some cases the Hypomanic Episodes themselves do not cause impairment; however, the impairment may result from the Major Depressive Episodes or from a chronic pattern of unpredictable mood episodes and fluctuating unreliable interpersonal and occupational functioning. The symptoms of Bipolar Disorder must not be better accounted for by a psychotic condition or due to the direct physiological effects of a medication, other somatic treatments for depression, drugs of abuse, or toxin exposure.

Bipolar Disorder is associated with a significant risk of completed suicide. Further, the patient suffering from Bipolar Disorder is likely to suffer from school truancy, school failure, occupational failure, or divorce.

Therefore, Bipolar Disorder is a serious, fairly prevelant, psychological condition which is clearly distinguished from psychotic conditions such as schizophrenia. DSM-IV, p. 353 (American Psychiatric

Association, Washington, D.C. 1994). DSM-IV, p. 353 (American Psychiatric Association, Washington, D.C. 1994).

It is known that olanzapine can provide antipsychotic activity and is currently undergoing investigation for this purpose. Olanzapine is a known compound and described in U.S. Patent No. 5,229,382 as being useful for the treatment of schizophrenia, schizophreniform disorder, acute mania, mild anxiety states, and psychosis. U.S. Patent No. 5,229,382 is herein incorporated by reference in its entirety. However, olanzapine was not known to be useful for the treatment of Bipolar Disorder. Applicants have discovered that olanzapine can be useful for the treatment of bipolar disorder. Olanzapine could address a long felt need for treatments which provide a favorable safety profile and effectively provide relief for the patient suffering from Bipolar Disorder.

Further, olanzapine can be useful for treating Bipolar Disorder, Major Depressive Episode. Thus, olanzapine can be a useful treatment for Bipolar Disorder wherein the Bipolar Disorder is not characterized by a manic episode.

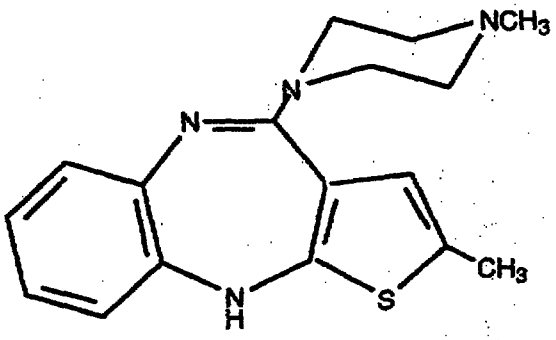
The presently claimed invention provides a method for treating bipolar disorder, comprising administering an effective amount of olanzapine or a pharmaceutically acceptable salt thereof to a patient in need of such treatment.

The present invention provides a method for treating depressive/depressive bipolar disorder, comprising administering an effective amount of olanzapine or a pharmaceutically acceptable salt thereof to a patient in need of such treatment.

Further, the present invention provides a method for treating Bipolar Disorder, Major Depressive episode, comprising administering an effective amount of olanzapine or a pharmaceutically acceptable salt thereof to a patient in need of such treatment.

A use of olanzapine for the manufacture of a medicament for therapeutic application in treating Bipolar Disorder.

Olanzapine is of the formula



(I)

or an acid addition salt thereof.

Generally, Bipolar Disorder involves at least one manic episode; however, some patients suffering from Bipolar Disorder experience Major Depressive episodes. The present invention provides a method for treating the patient suffering from or susceptible to Bipolar Disorder, wherein the patient fails to experience a manic episode.

It is especially preferred that olanzapine will be the Form II olanzapine polymorph having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874

4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

A typical example of an x-ray diffraction pattern for Form II is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

d	I/I_1
10.2689	100.00
8.577	7.96
7.4721	1.41
7.125	6.50
6.1459	3.12
6.071	5.12
5.4849	0.52
5.2181	6.86
5.1251	2.47

4.9874	7.41
4.7665	4.03
4.7158	6.80
4.4787	14.72
4.3307	1.48
4.2294	23.19
4.141	11.28
3.9873	9.01
3.7206	14.04
3.5645	2.27
3.5366	4.85
3.3828	3.47
3.2516	1.25
3.134	0.81
3.0848	0.45
3.0638	1.34
3.0111	3.51
2.8739	0.79
2.8102	1.47
2.7217	0.20
2.6432	1.26
2.6007	0.77

The x-ray diffraction patterns set out herein were obtained using a Siemens D5000 x-ray powder diffractometer having a copper K_α radiation source of wavelength, $\lambda = 1 \cdot 541$Å.

It is further preferred that the Form II olanzapine polymorph will be administered as the substantially pure Form II olanzapine polymorph.

As used herein "substantially pure" refers to Form II associated with less than about 5% Form I, preferably less than about 2% Form I, and more preferably less than about 1% Form I. Further, "substantially pure" Form II will contain less than about 0.5% related substances, wherein "related substances" refers to undesired chemical impurities or residual solvent or water.

The polymorph obtainable by the process taught in the '382 patent will be designated as Form I and has a typical x-ray powder diffraction pattern substantially as follows, obtained using a Siemens D5000 x-ray powder diffractometer, wherein d represents the interplanar spacing:

d
9.9463
8.5579
8.2445
6.8862
6.3787
6.2439
5.5895
5.3055
4.9815
4.8333
4.7255
4.6286
4.533
4.4624
4.2915
4.2346
4.0855
3.8254
3.7489
3.6983
3.5817
3.5064
3.3392
3.2806
3.2138
3.1118
3.0507
2.948
2.8172
2.7589

2.6597
2.6336
2.5956

A typical example of an x-ray diffraction pattern for Form I is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

d	I/I_1
9.9463	100.00
8.5579	15.18
8.2445	1.96
6.8862	14.73
6.3787	4.25
6.2439	5.21
5.5895	1.10
5.3055	0.95
4.9815	6.14
4.8333	68.37
4.7255	21.88
4.6286	3.82
4.533	17.83
4.4624	5.02
4.2915	9.19
4.2346	18.88
4.0855	17.29
3.8254	6.49
3.7489	10.64
3.6983	14.65
3.5817	3.04
3.5064	9.23
3.3392	4.67
3.2806	1.96
3.2138	2.52
3.1118	4.81
3.0507	1.96
2.948	2.40

2.8172	2.89
2.7589	2.27
2.6597	1.86
2.6336	1.10
2.5956	1.73

The x-ray powder diffraction patterns herein were obtained with a copper $K\alpha$ of wavelength λ = 1.541Å. The interplanar spacings in the column marked "d" are in Angstroms. The typical relative intensities are in the column marked "I/I_1".

As used herein, the term "mammal" shall refer to the Mammalia class of higher vertebrates. The term "mammal" includes, but is not limited to, a human. The term "treating" as used herein includes prophylaxis of the named condition or amelioration or elimination of the condition once it has been established.

As used herein, the term "Bipolar Disorder" shall refer to a condition characterized as a Bipolar Disorder, in the DSM-IV-R. Diagnostic and Statistical Manual of Mental Disorders, Revised, 3rd Ed. (1994) as catagory 296.xx. To further clarify, Applicants contemplate the treatment of both Bipolar Disorder I and Bipolar disorder II as described in the DSM-IV-R. The DSM-IV-R was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association, and provides clear descriptions of diagnostic catagories. 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.

The results of pharmacological studies show that olanzapine has muscarinic cholinergic receptor activity. The compound is active at the dopamine D-1 and D-2 receptors as indicated by an IC50 of less than 1 uM in the 3H-SCH233390 (Billard, et al. Life Sciences **35**:1885 (1984)) and the 3H spiperone (Seeman et al Nature **216**:717 (1976)) binding assays

respectively. Further, olanzapine is active at the 5-HT-2 receptor and 5-HT1C receptor. The complex pharmacological profile of the compound provides a medicament which can be useful for the treatment of Bipolar Disorder.

The usefulness of the compound for treating a Bipolar Disorder can be supported by the following studies as described.

I.

Clinical observations.

A double-blind multicenter clinical trial was designed to assess the safety and efficacy of olanzapine. Patients were randomized to olanzapine or placebo. The results of the study suggest that olanzapine can be useful for the treatment of Bipolar Disorder.

Olanzapine is effective over a wide dosage range, the actual dose administered being dependent on the condition being treated. For example, in the treatment of adult humans, dosages of from about 0.25 to 50 mg, preferably from 1 to 30 mg, and most preferably 1 to 20 mg per day may be used. A once a day dosage is normally sufficient, although divided doses may be administered. For treatment of a Bipolar Disorder, a dose range of from 1 to 30 mg, preferably 1 to 20 mg per day is suitable. Radiolabelled olanzapine, can be detected in the saliva and thus the compound can potentially be monitored in patients to assess compliance.

A preferred formulation of the invention is a solid oral formulation comprising from about 1 to about 20 mg or 1 to 10 mg of olanzapine as an effective amount of the active ingredient.

Most preferably, the solid oral formulation is contained in packaging materials which protect the formulation from moisture and light. For example, suitable packaging materials include amber colored high density polyethylene bottles, amber colored glass bottles, and other containers made of a material which inhibits the passage of

light. Most preferably, the packaging will include a desiccant pack. The container may be sealed with an aluminum foil blister to provide the desired protection and maintain product stability.

Olanzapine will normally be administered orally or by injection and, for this purpose, it is usually employed in the form of a pharmaceutical composition.

Accordingly, pharmaceutical compositions comprising olanzapine, as active ingredient associated with a pharmaceutically acceptable carrier may be prepared. In making the compositions of the invention conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. The active ingredient can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl-hydroxy-benzoate, talc, magnesium stearate or mineral oil. The compositions of the invention may, if desired, be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

Depending on the method of administration, the compositions for the treatment of central nervous system conditions may be formulated as tablets, capsules, injection solutions for parenteral use, gel or suspension for transdermal delivery, suspensions or elixirs for oral use or suppositories. Preferably the compositions are formulated in a unit dosage form, each dosage containing from 0.25 to 25 mg, more usually 1 to 20 mg, of the active

ingredient. An alternative preferred composition is a unit dosage form containing from 1 to 30 mg.

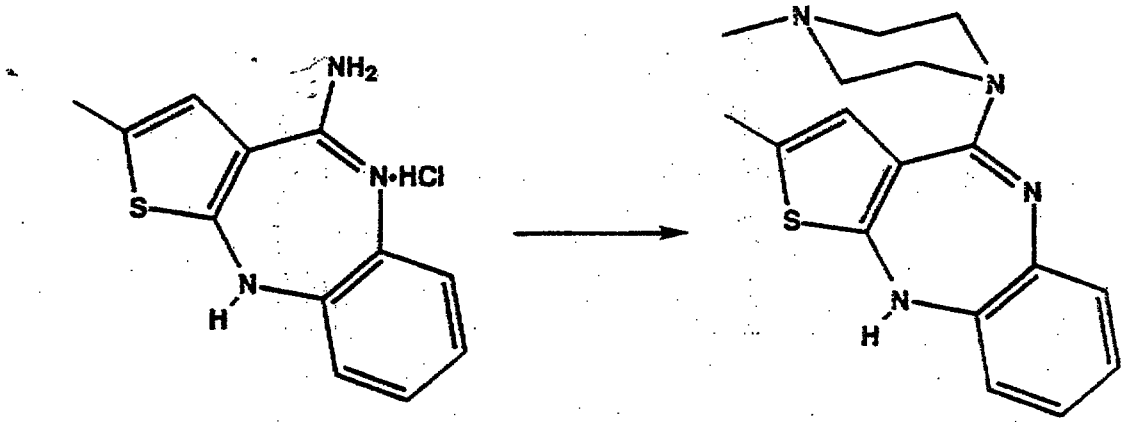
The materials for the present invention can be purchased or prepared by a variety of procedures well known to those of ordinary skill in the art. Olanzapine can be prepared as described by Chakrabarti in U.S. Patent No 5,229,382 ('382), herein incorporated by reference in its entirety. Further, the following preparations illustrate a method for preparing of the especially preferred Form II olanzapine polymorph.

Compound characterization methods include, for example, x-ray powder pattern analysis, thermogravimetric analysis (TGA), differential scanning calorimetery (DSC), titrametric analysis for water, and H^1-NMR analysis for solvent content.

The following examples are provided for purposes of illustration and are not to be construed as limiting the scope of the claimed invention.

Preparation 1

Technical Grade olanzapine



Intermediate 1

In a suitable three neck flask the following was added:

Dimethylsulfoxide (analytical): 6 volumes
Intermediate 1 : 75 g

N-Methylpiperazine (reagent) : 6 equivalents

Intermediate 1 can be prepared using methods known to the skilled artisan. For example, the preparation of the Intermediate 1 is taught in the '382 patent.

A sub-surface nitrogen sparge line was added to remove the ammonia formed during the reaction. The reaction was heated to 120°C and maintained at that temperature throughout the duration of the reaction. The reactions were followed by HPLC until ≤ 5% of the intermediate 1 was left unreacted. After the reaction was complete, the mixture was allowed to cool slowly to 20°C (about 2 hours). The reaction mixture was then transferred to an appropriate three neck round bottom flask and water bath. To this solution with agitation was added 10 volumes reagent grade methanol and the reaction was stirred at 20°C for 30 minutes. Three volumes of water was added slowly over about 30 minutes. The reaction slurry was cooled to zero to 5°C and stirred for 30 minutes. The product was filtered and the wet cake was washed with chilled methanol. The wet cake was dried in vacuo at 45°C overnight. The product was identified as technical olanzapine.

Yield: 76.7%; Potency: 98.1%

Preparation 2

Form II olanzapine polymorph

A 270 g sample of technical grade 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine was suspended in anhydrous ethyl acetate (2.7 L) . The mixture was heated to 76°C and maintained at 76°C for 30 minutes. The mixture was allowed to cool to 25°C. The resulting product was isolated using vacuum filtration. The product was identified as Form II using x-ray powder analysis.

Yield: 197 g.

The process described above for preparing Form II provides a pharmaceutically elegant product having potency ≥ 97%, total related substances < 0.5% and an isolated yield of > 73%.

EXAMPLE 1

A portion of the hydroxypropyl cellulose was dissolved in purified water to form a solution for granulation. The remaining hydroxypropyl cellulose (total of 4.0% w/w final tablet weight), which was an extra fine grade, was combined with the olanzapine (1.18% w/w), lactose (79.32% w/w) and a portion of the crospovidone (5% w/w) in a high shear granulator. All ingredients were security sieved prior to addition and dry blended in the granulator. This mixture was then granulated with the hydroxypropyl cellulose solution in the high shear granulator. The granulation was wet sized using standard methods. The wet granulation was then dried in a fluidized bed dryer and sized. The material was then added to a tumble bin mixer.

The running powders consisting of microcrystalline cellulose (granular) (10% w/w), magnesium stearate (0.5% w/w), and the remainder of the crospovidone were added to the sized granulation. The mixture was blended and compressed with the appropriate tooling on tablet compression equipment.

Subcoating:

Hydroxypropyl methylcellulose (10% w/w) was mixed with purified water to form a solution. Core tablets were divided into approximately equal sections and spray coated with the hydroxypropyl methylcellulose solution . The operation was performed in a perforated coating pan.

Coating of Core Tablets:

Color Mixture White (hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, and titanium dioxide) was mixed with purified water to form the coating suspension. Subcoated tablets were divided into approximately equal sections and spray coated with the coating suspension described above. The operation was performed in a perforated coating pan.

The coated tablets were lightly dusted with carnauba wax and imprinted with appropriate identification.



We Claim:

1. A method for treating Bipolar Disorder comprising administering to a mammal in need of such treatment, an effective amount olanzapine, or a pharmaceutically acceptable salt thereof.

2. A method of **Claim 1** wherein the Bipolar Disorder is Bipolar Disorder I.

3. A method of **Claim 2** wherein the Bipolar Disorder is Bipolar Disorder II.

4. A method of **Claim 1** wherein olanzapine is Form II olanzapine polymorph having a typical x-ray diffraction pattern as follows, wherein d represents the interplanar spacing:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638

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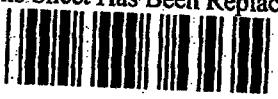

3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

5. A method of **Claim 2** wherein olanzapine is Form II olanzapine polymorph having a typical x-ray diffraction pattern as follows, wherein d represents the interplanar spacing:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

6. A method of **Claim** 3 wherein olanzapine is Form II olanzapine polymorph having a typical x-ray diffraction



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pattern as follows, wherein d represents the interplanar spacing:

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d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

7. A method of **Claim 1** wherein the effective amount is from about 1 mg to about 25 mg per day.

8. A method of **Claim 4** wherein the effective amount is from about 1 mg to about 20 mg per day.

9. A method for treating Bipolar Disorder, wherein the patient suffering from or susceptible to Bipolar Disorder does not experience mania, comprising admistering an



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effective amount olanzapine, or a pharmaceutically acceptable salt thereof to a patient in need thereof.

10. A method of **Claim 9** wherein olanzapine is Form II.

11. A method of **Claim 9** wherein the effective amount is from about 2.5 mg to about 30 mg per day.

12. A method for treating Bipolar Disorder, Major Depressive Episode, comprising admistering an effective amount olanzapine, or a pharmaceutically acceptable salt thereof to a patient in need thereof.

13. A method of **Claim 12** wherein the effective amount is from about 2.5 mg to about 30 mg per day.

14. A use of olanzapine for the manufacture of a medicament for therapeutic application in treating Bipolar Disorder.

15. A use of **Claim 14** wherein the Bipolar Disorder is Bipolar Disorder, Major Depressive Episode.

16. A use of Claim 14 wherein the patient does not experience a manic episode.

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We Claim:

1. A use of an effective amount olanzapine, or a pharmaceutically acceptable salt thereof in a preparation of a medicament for treating Bipolar Disorder in a subject in need thereof.

2. A use of Claim 1 wherein the Bipolar Disorder is Bipolar Disorder I.

3. A use of Claim 2 wherein the Bipolar Disorder is Bipolar Disorder II.

4. A use of Claim 1 wherein olanzapine is Form II olanzapine polymorph having a typical x-ray diffraction pattern as follows, wherein d represents the interplanar spacing:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
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3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

5. A use of Claim 2 wherein olanzapine is Form II olanzapine polymorph having a typical x-ray diffraction pattern as follows, wherein d represents the interplanar spacing:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

6. A use of Claim 3 wherein olanzapine is Form II olanzapine polymorph having a typical x-ray diffraction

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pattern as follows, wherein d represents the interplanar spacing:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

7. A use of Claim 1 wherein the effective amount is from about 1 mg to about 25 mg per day.

8. A use of Claim 4 wherein the effective amount is from about 1 mg to about 20 mg per day.

9. A use of an effective amount olanzapine, or a pharmaceutically acceptable salt thereof in a preparation of a medicament for treating Bipolar Disorder in a subject in need thereof, wherein said subject suffering from or susceptible to Bipolar Disorder does not experience mania.

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10. A use of **Claim 9** wherein olanzapine is Form II.

11. A use of **Claim 9** wherein the effective amount is from about 2.5 mg to about 30 mg per day.

12. A use of an effective amount olanzapine, or a pharmaceutically acceptable salt thereof in a preparation of a medicament for treating Bipolar Disorder and Major Depressive Episode in a subject in need thereof.

13. A use of **Claim 12** wherein the effective amount is from about 2.5 mg to about 30 mg per day.

14. A use of olanzapine for the manufacture of a medicament for therapeutic application in treating Bipolar Disorder.

15. A use of **Claim 14** wherein the Bipolar Disorder is Bipolar Disorder, Major Depressive Episode.

16. A use of **Claim 14** wherein the subject does not experience a manic episode.

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WE CLAIM :

1. A use of an effective amount olanzapine, or a pharmaceutically acceptable salt thereof in a preparation of a medicament for treating Bipolar Disorder I in a subject in need thereof.

2. A use of an effective amount olanzapine, or a pharmaceutically acceptable salt thereof in a preparation of a medicament for treating Bipolar Disorder II in a subject in need thereof.

3. A use of Claim 1 wherein olanzapine is Form II olanzapine polymorph having a typical x-ray diffraction pattern as follows, wherein d represents the interplanar spacing :

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638

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3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

4. A use of Claim 2 wherein olanzapine is Form II olanzapine polymorph having a typical x-ray diffraction pattern as follows, wherein d represents the interplanar spacing :

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

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5. A use of Claim 1 or 2 wherein the effective amount is from about 1 mg to about 25 mg per day.

6. A use of Claim 1 or 2 wherein the effective amount is from about 1 mg to about 20 mg per day.

7. A use of an effective amount olanzapine, or a pharmaceutically acceptable salt thereof in a preparation of a medicament for treating Bipolar Disorder I or Bipolar Disorder II in a subject in need thereof, wherein said subject suffering from or in need thereof, wherein said subject suffering from or susceptible to Bipolar Disorder I or II does not experience mania.

8. A use of Claim 7 wherein olanzapine is Form II.

9. A use of Claim 7 wherein the effective amount is from about 2.5 mg to about 30 mg per day.

10. A use of an effective amount olanzapine, or a pharmaceutically acceptable salt thereof in a preparation of a medicament for treating Bipolar Disorder I or II and Major Depressive Episode in a subject in need thereof.

11. A use of Claim 10 wherein the effective amount is from about 2.5 mg to about 30 mg per day.

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12. A use of olanzapine for the manufacture of a medicament for therapeutic application in treating Bipolar Disorder I or II.

13. A use of Claim 12 wherein the Bipolar Disorder is Bipolar Disorder I or II, Major Depressive Episode.

14. A use of Claim 13 wherein the subject does not experience a manic episode.

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(54) Title: METHOD FOR TREATING BIPOLAR DISORDER

(57) Abstract

The invention provides a method for treating bipolar disorder comprising administering an effective amount of olanzapine to a patient in need thereof. Additionally, the present invention provides a method for treating Bipolar Disorder, Major Depressive Episode.