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(54) Title: ENDOXIFEN FOR THE TREATMENT OF BIPOLAR I DISORDER

(57) Abstract: A method for maintaining a therapeutically effective concentration of endoxifen for treatment of a patient with bipolar I disorder is provided. The said method includes administering to the patient, a dose of 2 mg to 16 mg of endoxifen citrate in an enteric coated tablet once per day for at least 21 days. Further, the patient is not required to be administered rescue medication during the administration of the endoxifen citrate.

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ENDOXIFEN FOR THE TREATMENT OF BIPOLAR I DISORDER

FIELD OF THE INVENTION

The present disclosure relates to a method for maintaining a therapeutically effective concentration of endoxifen for treatment of a patient with bipolar I disorder, wherein the said method comprises administering to the patient, a dose of 2 mg to 16 mg of endoxifen citrate in an enteric coated tablet once per day for at least 21 days. Further, the patient is not required to be administered rescue medication during the administration of the endoxifen citrate.

BACKGROUND OF THE INVENTION

Bipolar disorder is currently a major health problem. Bipolar disorder is a chronic, debilitating illness that affects up to 3 % of the US population. It causes significant morbidity and imposes a burden on the society. The causes of bipolar disorder are still unknown, and no agent has been specifically developed on the basis of an understanding of the pathophysiology of the illness or mechanism of action for effective treatments.

Several drugs have been approved for treatment of bipolar disorder, such as lithium, valproate or divalproex sodium, carbamazepine, and atypical antipsychotics for the treatment of acute bipolar mania. While these drugs have provided relief for many individuals with bipolar disorder, significant issues with tolerability, efficacy, and attempt suicide or have suicidal behaviour still remain. Further, there is also a need of rescue medications. Divalproex has a good tolerability but a high discontinuation rate. There is also a continuous need to observe the therapeutic dose monitoring in patients during the treatment. The clinicians, for example, may find themselves in situations in which better tolerated agents are less effective, and vice versa. Also, the adherence to the treatment is affected by adverse effects such as sedation, weight gain, thrombocytopenia, and thyroid disorders.

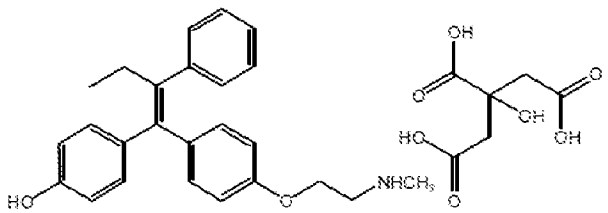
Available treatments help a substantial proportion of patients, but are not beneficial for an estimated 40-50 % of the population.

SUMMARY OF THE INVENTION

Protein kinase C (PKC) appears to have a role in bipolar disorder. PKC is involved in controlling the function of proteins through the phosphorylation of hydroxyl groups of serine and threonine amino acid residues on these proteins, which are known to play a vital role in cell signalling pathways. It regulates multiple neuronal processes implicated in mood regulation. In current clinical practice, mood stabilizers and antidepressants have been shown to modulate the PKC pathway. Disrupted PKC activity has been found both in post-mortem brains and platelet from patients with mood disorders. Accumulating evidence suggests an imbalance of the PKC signalling system in mood disorders. Thus, PKC is considered as a novel molecular target for the development of innovative medicine for bipolar disorder.

Targeting the PKC signalling pathway for bipolar disorder can improve the patient compliance, when therapeutic dose monitoring is not required in patient, and such treatment can provide significant improvement in mania and depression.

Endoxifen is a non-steroidal selective estrogen receptor modulator (SERM) of the triphenylethylene group. It is an active metabolite of tamoxifen and has been found to be effective in patients that have failed previous hormonal therapies (tamoxifen, aromatase inhibitors, and fulvestrant). The prodrug tamoxifen is metabolized by the CYP2D6 enzyme to produce afimoxifene (4-hydroxytamoxifen) and endoxifen. The chemical name of endoxifen citrate is (Z) – 1 - (4-Hydroxyphenyl) - 1- {4 - [2 -(monomethylamino) ethoxy] phenyl} – 2 – pheny l -1-butene citrate. The empirical formula of endoxifen citrate is $C_{25}H_{27}NO_2$–$C_6H_8O_7$, and has following chemical structure as given below (formula I):



(I)

The exact mechanism by which endoxifen exerts its therapeutic effects have not been established in bipolar disorder. However, the efficacy of endoxifen could be mediated through

PKC. The PKC represents a family of enzymes highly enriched in brain, where it plays a major role in regulating both pre- and post-synaptic aspects of neurotransmission. Excessive activation of PKC results in symptoms related to bipolar disorder. The PKC signalling pathway is clearly a target for the actions of two structurally dissimilar antimanic agents – lithium and valproate. Tamoxifen, a widely used breast cancer drug is also known to inhibit PKC and demonstrate antimanic properties in human. Endoxifen exhibited four-fold higher potency compared to tamoxifen in inhibiting the PKC activity and is not dependent on the isozyme cytochrome P450 2D6 (CYP2D6) for action on the target tissues. Endxifen is a PKC inhibitor and is effective in the treatment of bipolar disorder. Further, endoxifen has a broad therapeutic index as compared to divalproex sodium.

An object of the present disclosure is to provide a method for maintaining a therapeutically effective concentration of endoxifen for treatment of bipolar I disorder in a patient.

Another object of the present disclosure is to provide a method for maintaining a therapeutically effective concentration of endoxifen for treatment of bipolar I disorder in a patient, wherein the patient has manic episodes with or without mixed features.

Another object of the present disclosure is to provide a method for maintaining a therapeutically effective concentration of endoxifen for treatment of bipolar I disorder in a patient, wherein the patient has depression or associated with depressive episodes.

Another object of the present disclosure is to provide a method for maintaining a therapeutically effective concentration of endoxifen for the treatment of patient with bipolar I disorder, wherein the method comprises administering to the patient, a dose of 2 mg to 16 mg of endoxifen citrate in an enteric coated tablet once per day.

Another object of the present disclosure is to provide a method for maintaining a therapeutically effective concentration of endoxifen for the treatment of patient with bipolar I disorder, wherein the method comprises administering to the patient, a dose of 2 mg to 16 mg of endoxifen citrate in an enteric coated tablet once per day for at least 21 days.

Another object of the present disclosure is to provide a method for maintaining a therapeutically effective concentration of endoxifen for the treatment of patient with bipolar I

disorder, wherein the method comprises administering to the patient, a dose of 2 mg to 16 mg of endoxifen citrate in an enteric coated tablet once per day for at least 21 days, wherein the patient does not require rescue medication.

The objects described herein are directed to a method for maintaining a therapeutically effective concentration of endoxifen for treatment of a patient with bipolar I disorder, wherein the method comprises administering to the patient, a dose of 2 mg to 16 mg of endoxifen citrate in an enteric coated tablet once per day for at least 21 days. Further, the said method as per the present disclosure, wherein the patient does not require rescue medication.

DETAILED DESCRIPTION OF THE INVENTION

All terms as used herein in this application, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. Other more specific definitions for certain terms as used in the present application are as set forth below and are intended to apply uniformly throughout the specification and claims unless an otherwise expressly set out definition provides a broader definition.

For the purposes of the present application, any ranges given include both the lower and the upper end points of the range. Ranges given should be considered approximate, unless specifically stated.

The term “EOT” refers to end of treatment.

The term “therapeutically effective concentration” refers to a concentration of endoxifen in plasma which is sufficient to decrease or prevent or cure the symptoms associated with a medical condition or infirmity or to normalize body functions in disease or disorders that result in impairment of specific bodily functions.

The term "rescue medication" refers to an additional medication necessary to treat breakthrough or recurring symptoms. For present disclosure, the rescue medications are selected from the group of lithium, valproate, lamotrigine, benzodiazepines, anticholinergics and like thereof.

The term "enteric coating" refers to any pharmaceutically acceptable coating preventing the release of the active agent in the stomach and sufficiently disintegrating in the intestine tract (by contact with approximately neutral or alkaline intestine juices) to allow the resorption of the active agent through the walls of the intestinal tract. The enteric coating remains intact in the acidic environment of the stomach and then solubilize in the more alkaline environment of the small intestine. Generally speaking, enteric coating helps in preventing gastric mucosal irritation and can be used for acid labile drugs which gets denatured in acidic medium.

In one embodiment the present application provides a method for maintaining a therapeutically effective concentration of endoxifen for treatment of bipolar I disorder in a patient.

In another embodiment the present application provides a method for maintaining a therapeutically effective concentration of endoxifen for treatment of bipolar I disorder in a patient.

In another embodiment the present application provides a method for maintaining a therapeutically effective concentration of endoxifen for treatment of bipolar I disorder in a patient, wherein the patient has manic episodes with or without mixed features.

In another embodiment the present application provides a method for maintaining a therapeutically effective concentration of endoxifen for treatment of bipolar I disorder in a patient, wherein the patient has depression or associated with depressive episodes.

In another embodiment the present application provides a method for maintaining a therapeutically effective concentration of endoxifen for the treatment of patient with bipolar I disorder, wherein the method comprises administering to the patient, a dose of 2 mg to 16 mg of endoxifen citrate in an enteric coated tablet once per day.

In another embodiment the present application provides a method for maintaining a therapeutically effective concentration of endoxifen for the treatment of patient with bipolar I disorder, wherein the method comprises administering to the patient, a dose of 2 mg to 16 mg of endoxifen citrate in an enteric coated tablet once per day for at least 21 days.

In another embodiment of the present application is to provide a method for maintaining a therapeutically effective concentration of endoxifen for the treatment of patient with bipolar I disorder, wherein the method comprises administering to the patient, a dose of 2 mg to 16 mg of endoxifen citrate in an enteric coated tablet once per day for at least 21 days, wherein the patient does not require rescue medication.

The embodiments described herein are directed to a method for maintaining a therapeutically effective concentration of endoxifen for treatment of a patient with bipolar I disorder, wherein the method comprises an administering to the patient, a dose of 2 mg to 16 mg of endoxifen citrate in an enteric coated tablet once per day for at least 21 days. Further, the said method as per the present disclosure, wherein the patient does not require rescue medication.

The present application has been described by way of example only, and it is to be recognized that modifications thereto falling within the scope, and spirit of appended claims, and which would be obvious to a person skilled in the art based upon the disclosure herein, are also considered to be within the scope of this disclosure.

Clinical study data:

Clinical study of an enteric coated tablet comprising endoxifen citrate formulation was carried out by administering to the patient doses of 2 mg to 16 mg of endoxifen citrate in an enteric coated tablet once per day for at least 21 days according to the present application.

Design of the study:

The clinical study was a multicenter, randomized, double-blind, double-dummy, active controlled, parallel study to assess the efficacy and safety of endoxifen enteric coated tablet 8 mg and divalproex sodium extended release tablet 1000 mg in patients of bipolar I disorders.

Total 228 patients were enrolled in the study. All 228 patients were qualified for safety trial.

At the EOT, none of the patient required rescue medications, no rescue medications were administered to any of the patients, and none of the patient discontinue from the study.

CLAIMS

1. A method for maintaining a therapeutically effective concentration of endoxifen for treatment of a patient with bipolar I disorder, said method comprising:

   administering to the patient, a dose of 2 mg to 16 mg of endoxifen citrate in an enteric coated tablet once per day for at least 21 days; wherein the patient is not administered rescue medication during the said treatment.

2. The method of claim 1, wherein the patient has manic episodes with mixed features.

3. The method of claim 1, wherein the patient has manic episodes without mixed features.

4. The method of claim 1, wherein the patient has depression.

5. The method of claim 1, wherein the patient associated with depressive episodes.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/052972

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/138(2006.01)i; **A61P 25/18**(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 31/138(2006.01); A61K 31/00(2006.01); A61K 31/135(2006.01); A61K 31/4196(2006.01); A61K 31/7072(2006.01); A61K 9/06(2006.01); A61K 9/19(2006.01); A61P 25/24(2006.01)

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

Korean utility models and applications for utility models
Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) & keywords: endoxifen, bipolar I disorder, dose, periods, manic, depression

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2019-0231687 A1 (JINA PHARMACEUTICALS, INC.) 01 August 2019 (2019-08-01) claims 1, 3, 6, 7, 9, 14; and paragraphs [0009], [0057], [0170]	1-5
A	AHMAD, A. et al., `Endoxifen, a New Treatment Option for Mania: A Double-Blind, Active-Controlled Trial Demonstrates the Antimanic Efficacy of Endoxifen`, Clin. Transl. Sci., 2016, Vol.9, pp.252-259 the whole document	1-5
A	US 2012-0201908 A1 (MILLER, K. P.) 09 August 2012 (2012-08-09) the whole document	1-5
A	WO 2009-152430 A2 (REPLIGEN CORPORATION) 17 December 2009 (2009-12-17) the whole document	1-5
A	WO 2008-048194 A1 (YESILOGLUJ. A. Y.) 24 April 2008 (2008-04-24) the whole document	1-5

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2021	**15 July 2021**

Name and mailing address of the ISA/KR	Authorized officer
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
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