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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 July 2013 (04.07.20 13)

W IPO | PCT

(10) International Publication Number
WO 2013/100870 Al

(51) International Patent Classification:
A61K 9/46 (2006.01) *A61P 25/22* (2006.01)
A61K 9/20 (2006.01) *A61P 25/24* (2006.01)
A61K 31/343 (2006.01) *A61P 25/32* (2006.01)

(21) International Application Number:
PCT/TR20 12/000205

(22) International Filing Date:
3 December 2012 (03.12.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
201 1/1 1953 2 December 201 1 (02. 12.201 1) TR

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2013/100870 A1

(54) Title: NEW ANTIPSYCHOTIC COMPOSITIONS

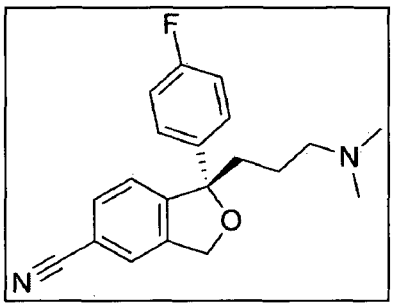
(57) Abstract: The present invention relates to pharmaceutical compositions comprising escitalopram and fields of use thereof.

NEW ANTIPSYCHOTIC COMPOSITIONS

The present invention relates to pharmaceutical compositions comprising escitalopram and fields of use thereof.

Citalopram which was first disclosed in the patent numbered DE2657 013 is a selective serotonin reuptake inhibitor. The average daily dose of citalopram is 20 mg, and it is marketed in citalopram hydrobromide and citalopram hydrochloride salt forms.

Pharmaceutically more effective (S)-enantiomer of citalopram is escitalopram with the molecule formula (S)- l-[3-(dimethylamino)propyl]- 1-(4-fluorophenyl)- l,3-dihydroisobenzofuran-5-carbonitrile which was first disclosed in the patent numbered US 4 943 590.



Formula (I)

The active agent is sold in 10 and 20 mg film coated tablet and oral solution dosage forms on the market. Said drug is used in the treatment of acute and major depressive diseases in adults and adolescents aged between 12 and 17.

However, escitalopram is a very low-soluble active agent and this low solubility of the active agent reduces the therapeutically effective dose taken by the patient.

In this case, the patients increase the dose of the drug in order to obtain therapeutic effect that they need. However, increased drug dose increase the possibility of side effects and therefore it is not generally preferred.

In other aspect, the pharmaceutical compositions comprising escitalopram are not applicable to all types of dosage forms due to low solubility of the active agent. For instance, when water soluble dosage forms are developed, it is quite difficult to obtain the required solubility characteristics.

As a result of the studies they conducted in order to improve solubility characteristics of the active agent, the inventors have found that solubility characteristics can be improved in the pharmaceutical compositions prepared by using an active agent having an average particle size (d_{50}) less than 20 μηι and a (d_{50}) / (d_{95}) particle size ratio less than 1.

The term "average particle size" used herein refers to average particle size by volume and it is also shown with d_{50} in short. In this sense, the term d_{50} signifies that half of the said substance by volume has a particle size over the value stated with d_{50} and the other half of the substance by volume has a particle size below the value stated with $d_{50.}$

The term d_{95} signifies that **95%** of the said substance by volume has a particle size below the stated value and **5%** of the said substance by volume has a particle size over the stated value.

D_{50} and d_{95} particle sizes of the active agent comprised in the pharmaceutical compositions according to the present invention can be measured with one of the known measuring devices, for instance with a device which measures particle distribution by laser diffraction (for instance, Malvern Mastersizer etc.).

The pharmaceutical compositions according to the present invention comprising escitalopram having a particle size (d_{50}) less than 20 μm and a (d_{50}) / (d_{95}) particle size ratio less than 1 can be prepared in any dosage forms such as tablet, effervescent tablet, effervescent granule, effervescent dry powder, film coated tablet, enterically coated tablet, dry powder, granule, capsule, prolonged release tablet, modified release tablet, delayed release tablet.

In the case that the pharmaceutical compositions according to the present invention are in tablet dosage form, the obtained tablets can optionally be presented in film coated tablet form. The film coating solution that can be used for film coating of the formulations according to the present invention comprises at least one excipient that can be selected from cellulose derivatives such as hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, methyl hydroxyethyl cellulose and sodium carboxymethyl cellulose; and synthetic polymers such as polyvinyl acetal diethyl amino acetate, amino alkyl methacrylate copolymers and polyvinylpyrrolidone and polysaccharides such as pullulan or combinations thereof.

An advantage of the pharmaceutical compositions of the present invention is that the formulations can be prepared optionally in water soluble dosage forms such as effervescent tablet. Said water soluble dosage forms can be effervescent or non-effervescent.

The term "escitalopram" used throughout the text refers to said active agent's pharmaceutically acceptable salts, enantiomers, racemates, solvates, hydrates, different polymorphic forms, amorphous and crystalline forms or combinations thereof. Though, the active agent used in the compositions of the present invention is preferably escitalopram oxalate salt.

A characteristic feature of the pharmaceutical compositions of the present invention comprising escitalopram having a particle size (d_{50}) less than 20 μm and a (d_{50}) / (d_{95}) particle

size ratio less than 1 is that said pharmaceutical compositions comprise at least one pharmaceutically acceptable excipient in addition to the active agent.

The excipients that can be used in the pharmaceutical compositions of the present invention comprising escitalopram having a particle size (d_{50}) less than 20 μm and a (d_{50}) / (d_{95}) particle size ratio less than 1 can be selected from a group comprising binders, disintegrants, viscosity enhancing agents, filling agents, drying agents, surfactants, stabilizing agents, oiling agents, lubricants, diluents, glidants, wetting agents, coating agents designed in order to provide various release characteristics, pH regulators, effervescent acids, effervescent bases, gelling agents, flavouring agents, sweeteners, emulgators, anti-foaming substances, protective agents, solvent or solvent mixtures, colouring agents and complexing agents or combinations thereof.

The disintegrants that can be used in the pharmaceutical compositions of the present invention comprising escitalopram having a particle size (d_{50}) less than 20 μm and a (d_{50}) / (d_{95}) particle size ratio less than 1 can be selected from a group comprising carboxymethyl cellulose, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium, croscarmellose sodium, crospovidone, hydroxypropyl cellulose, microcrystalline cellulose, methyl cellulose, chitosan, starch, sodium starch glycolate or combinations thereof.

The diluents that can be used in the pharmaceutical compositions of the present invention comprising escitalopram having a particle size (d_{50}) less than 20 μm and a (d_{50}) / (d_{95}) particle size ratio less than 1 can be selected from a group comprising calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, microcrystalline cellulose, dextrose, fructose, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrin, maltose, mannitol, simethicone, sorbitol, starch and starch derivatives (for instance corn starch), sodium chloride, sucrose, talc, xylitol or the combinations thereof.

The lubricants that can be used in the pharmaceutical compositions of the present invention comprising escitalopram having a particle size (d_{50}) less than 20 μm and a (d_{50}) / (d_{95}) particle size ratio less than 1 can be selected from a group comprising calcium stearate, magnesium stearate, polyethylene glycol, sodium benzoate, potassium benzoate, sodium lauryl sulphate, talc, stearic acid, zinc stearate or combinations thereof.

The oiling agents that can be used in the pharmaceutical compositions of the present invention comprising escitalopram having a particle size (d_{50}) less than 20 μm and a (d_{50}) / (d_{95}) particle size ratio less than 1 can be selected from a group comprising tribasic calcium phosphate, colloidal silicone dioxide, magnesium silicate, magnesium trisilicate, talc or combinations thereof.

The binders that can be used in the pharmaceutical compositions of the present invention comprising escitalopram having a particle size (d_{50}) less than 20 μπι and a (d_{50}) / (d_{95}) particle size ratio less than 1 can be selected from a group comprising carboxymethyl cellulose sodium, ethyl cellulose, gelatine, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hypromellose, magnesium aluminium silicate, maltodextrin, methyl cellulose, povidone, starch or combinations thereof.

The effervescent acids that can be used in the pharmaceutical compositions of the present invention comprising escitalopram having a particle size (d_{50}) less than 20 μη and a (d_{50}) / (d_{95}) particle size ratio less than 1 can be selected from a group comprising organic acids such as malic acid, citric acid, tartaric acid, fumaric acid, maleic acid or hydrates, anhydrates or combinations thereof.

The effervescent bases that can be used in the pharmaceutical compositions of the present invention comprising escitalopram having a particle size (d_{50}) less than 20 μηι and a (d_{50}) / (d_{95}) particle size ratio less than 1 can be selected from a group comprising sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate or combinations thereof.

The pH regulating agents that can be used in the pharmaceutical compositions of the present invention comprising escitalopram having a particle size (d_{50}) less than 20 μηι and a (d_{50}) / (d_{95}) particle size ratio less than 1 can be selected from a group comprising citrate, phosphate, carbonate, tartrate, fumarate, acetate, maleate and amino acid salts or combinations thereof.

The surfactants that can be used in the pharmaceutical compositions of the present invention comprising escitalopram having a particle size (d_{50}) less than 20 μm and a (d_{50}) / (d_{95}) particle size ratio less than 1 can be selected from a group comprising sodium lauryl sulphate, polysorbate, polyoxyethylene, polyoxypropylene glycol or combinations thereof.

The stabilizing agents that can be used in the pharmaceutical compositions of the present invention comprising escitalopram having a particle size (d_{50}) less than 20 μηι and a (d_{50}) / (d_{95}) particle size ratio less than 1 can be selected from a group comprising tocopherol, tetrasoidum edetate, nicotinamide, cyclodextrin or combinations thereof.

The sweetener and/or taste regulating agents that can be used in the pharmaceutical compositions of the present invention comprising escitalopram having a particle size (d_{50}) less than 20 μπι and a (d_{50}) / (d_{95}) particle size ratio less than 1 can be selected from a group comprising acesulfame, aspartame, dextrose, fructose, maltitol, maltose, mannitol, saccharine, saccharine sodium, sodium cyclamate, sorbitol, sucralose, sucrose, xylitol, sodium chloride or combinations thereof.

The flavouring agents that can be used in the pharmaceutical compositions of the present invention comprising escitalopram having a particle size (d_{50}) less than 20 μπι and a (d_{50}) / (d_{95}) particle size ratio less than 1 can be selected from a group comprising menthol, lemon, orange, vanilla, strawberry, raspberry, caramel or combinations thereof.

A characteristic feature of the pharmaceutical compositions of the present invention comprising escitalopram as the active agent is that particle size (d_{50}) of the active agent is less than 15 μη and the ratio of (d_{50}) / (d_{95}) particle sizes of the active agent is less than 0.75.

Another characteristic feature of the pharmaceutical compositions of the present invention comprising escitalopram as the active agent is that particle size (d_{50}) of the active agent is less than 13 μη and the ratio of (d_{50}) / (d_{95}) particle sizes of the active agent is less than 0.75.

Another characteristic feature of the pharmaceutical compositions of the present invention comprising escitalopram as the active agent is that particle size (d_{50}) of the active agent is in the range of 1 μηι to 13 μm and the ratio of (d_{50}) / (d_{95}) particle sizes of the active agent is less than 0.50.

A characteristic feature of the pharmaceutical compositions of the present invention comprising escitalopram as the active agent is that said pharmaceutical compositions comprise the active agent in the range of 0.1 to 10% by weight, preferably in the range of 0.1 to 5% by weight.

The pharmaceutical compositions of the present invention can be produced by one of the methods in the prior art. Wet granulation, dry granulation, dry blending, direct compression methods can be listed among these production methods. One or more of these methods can be used together for production of the compositions.

The pharmaceutical compositions of the present invention can be used in the treatment and/or prevention of depression (major depressive disorder), geriatrics, obesity, alcoholism, neurotic disorders, anxiety disorder [Agoraphobia (aeroacrophobia) or non-agoraphobia panic disorder, social anxiety disorder, generalized anxiety disorder and obsessive compulsive disorder], post-traumatic stress disorder, panic attack.

The examples below are given in order to explain the pharmaceutical compositions of the present invention; yet, the pharmaceutical compositions of the present invention are not limited to these examples.

EXAMPLES

1. Tablet

Content	**(%) of Amount in Unit Dose**
Escitalopram Oxalate (d_{50} / d_{90}: 0.6)	15
Diluent	75
Disintegrate	5
Lubricant	0.50
Sweetener	4.50
Total	**100**

Escitalopram, disintegrant and diluent are mixed for production of the formulation given. The sweetener is added into the mixture and then the mixture is treated with the lubricant. The final mixture obtained is compressed into tablets. The tablets obtained can optionally be film-coated with film coated agent

2. Effervescent Granule

Content	**(%) of Amount in Unit Dose**
Escitalopram Oxalate (d_{50} / d_{90}: 0.5)	1.00
Effervescent couple	86.00
Lubricant	1.00
Filling agent	5.00
Binder	3.00
Sweetener	1.50
Flavouring Agent	1.50
Total	**100**

In order to obtain the effervescent granule composition given, escitalopram and effervescent couple are wet-granulated with the granulation solution comprising the filling agent and the binder. The obtained granules are dried and the sweetener, flavouring agent and then lubricant are added into the granules.

The granules can optionally be compressed in tablet form.

CLAIMS

1) A pharmaceutical composition comprising escitalopram, characterized in that the active agent has a d_{50} particle size less than 20 μm and a (d_{50}) / (d_{95}) particle size ratio less than 1.

2) The pharmaceutical composition according to claim 1, characterized in that d_{50} particle size of the active agent is less than 15 μm and (d_{50}) / (d_{95}) particle size ratio of the active agent is less than 0.75.

3) The pharmaceutical composition according to claim 2, characterized in that d_{50} particle size of the active agent is less than 13 μm and (d_{50}) / (d_{95}) particle size ratio of the active agent is less than 0.75.

4) The pharmaceutical composition according to claim 2 or 3, characterized in that d_{50} particle size of the active agent is in the range of 1 μm to 13 μm and (d_{50}) / (d_{95}) particle size ratio of the active agent is less than 0.50.

5) The pharmaceutical composition according to any preceding claims, characterized in that escitalopram used in the compositions is in the form of its pharmaceutically acceptable salts, enantiomers, racemates, solvates, hydrates, different polymorphic forms, amorphous and crystalline forms or combinations thereof.

6) The pharmaceutical composition according to claim 5, characterized in that escitalopram is in its oxalate salt form.

7) The pharmaceutical composition according to any preceding claims, characterized in that said composition is in any dosage forms such as tablet, effervescent tablet, effervescent granule, effervescent dry powder, film coated tablet, enterically coated tablet, dry powder, granule, capsule, prolonged release tablet, modified release tablet, delayed release tablet.

8) A dosage form according to claim 7, characterized in that in the case that said dosage form is in tablet form, the tablets can optionally be film coated.

9) A dosage form according to claim 7, characterized in that, said dosage form is optionally in the form of effervescent.

10) The pharmaceutical composition according to any preceding claims, characterized in that said composition comprises at least one pharmaceutically acceptable excipient in addition to the active agent.

11) The pharmaceutical composition according to claim 8, characterized in that said composition comprises at least one pharmaceutically acceptable excipient selected from a group comprising disintegrants, viscosity enhancing agents, filling agents,

drying agents, surfactants, stabilizing agents, oiling agent, lubricants, diluents, glidants, wetting agents, coating agents designed in order to provide various release characteristics, pH regulators, effervescent acids, effervescent bases, gelling agents, flavouring agents, sweeteners, emulgators, anti-foaming agents, protective agents, solvent or solvent mixtures, colouring agents and complexing agents or combinations thereof.

12) The pharmaceutical composition according to claim 11, characterized in that the effervescent acid used in said compositions is selected from a group comprising organic acids such as malic acid, citric acid, tartaric acid, fumaric acid, maleic acid; hydrates, anhydrates or combinations thereof.

13) The pharmaceutical composition according to claim 11, characterized in that the effervescent base used in said compositions is selected from a group comprising sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate or combinations thereof

14) The pharmaceutical composition according to any preceding claims characterized in that said composition comprises escitalopram in the range of 0.1 to 10% by weight, which has a d_{50} particle size less than 20 μm and a (d_{50}) / (d_{95}) particle size ratio less than 1.

15) The pharmaceutical composition according to claim 14, characterized in that said composition comprises escitalopram in the range of 0.1 to 5% by weight, which has a d_{50} particle size less than 20 μm and a (d_{50}) / (d_{95}) particle size ratio less than 1.

16) The pharmaceutical composition according to any preceding claims, characterized in that said composition is used in the treatment and/or prevention of depression (major depressive disorder), geriatrics, obesity, alcoholism, neurotic disorders, anxiety disorder [Agoraphobia (aeroacrophobia) or non-agoraphobia panic disorder, social anxiety disorder, generalized anxiety disorder and obsessive compulsive disorder], post-traumatic stress disorder, panic attack.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2012/000205

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/46 A61K9/20 A61K31/343 A61P25/22 A61P25/24
A61P25/32
ADD.
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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal , BIOSIS, EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 2009/048336 A1 (KOLLA NAVEEN KUMAR [IN] ET AL) 19 February 2009 (2009-02-19) page 2, paragraph 0031 - page 3, paragraph 0054 page 4; table 1 example 2 -----	1-11 , 14-16 12 , 13
Y	WO 2007/050697 A2 (ALAMO PHARMACEUTICALS LLC [US] ; CUTLER NEAL R [US]) 3 May 2007 (2007-05-03) page 13, paragraph 4 page 24, paragraph 4 - page 25, paragraph 2 claims 1, 6, 7, 19 -----	12 , 13

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" documentwhich may throw doubts on priority claim(s) orwhich is cited to establish the publication date of another citation or other special reason (as specified)

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 May 2013	07/06/2013

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/TR2012/000205

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2009048336 A1	19-02-2009	NONE	
W0 2007050697 A2	03-05-2007	EP 1991234 A2	19-11-2008
		US 2007092586 A1	26-04-2007
		W0 2007050697 A2	03-05-2007