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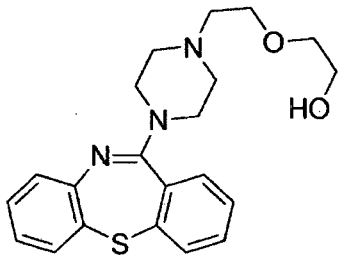
(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING QUETIAPINE

(57) Abstract: The present invention relates to pharmaceutical formulations comprising quetiapine that shall be used in schizophrenia, depressive episodes related to bipolar disorder, acute manic episodes related to bipolar disorder and in continuous treatment of bipolar disorders.

PHARMACEUTICAL COMPOSITIONS COMPRISING QUETIAPINE

The present invention relates to pharmaceutical formulations comprising quetiapine that shall be used in schizophrenia, depressive episodes related to bipolar disorder, acute manic episodes related to bipolar disorder and in continuous treatment of bipolar disorders.

Quetiapine was first disclosed in the application numbered US4879288. In said document, it has been disclosed that quetiapine is effective in schizophrenia, depressive episodes related to bipolar disorder, acute manic episodes related to bipolar disorder and in continuous treatment of bipolar disorders.



Quetiapine is available in film tablet forms comprising 25, 100, 200, 300 mg quetiapine or prolonged release tablet forms comprising 50, 200, 300, 400 mg quetiapine on the market.

During preparation of formulations comprising quetiapine, it is seen that the formulation adheres to machine parts such as inner walls of the die and the punch. This situation causes some part of the medicament to remain on the punches and in the dies, which brings some problems to the manufacturers during preparation phase of the medicament. In addition, since some part of the medicament remains on the punches and in the dies, the dosage form obtained does not have the desired shape and desired smoothness and this brings some problems at quality control phases. Furthermore, in the case that the formulations are compressed in tablet form, machine parts present corrosion and wear in time due to the friction between tablet surface and punch or inner wall of the die during ejection of the tablets. Therefore, these problems seen during preparation of the formulations comprising quetiapine pose problems for manufacturers at production and quality control phases and impede to obtain the final product effectively.

As it is seen, there is need for development of new approaches in order to obtain medicaments comprising quetiapine which are produced in the manner that no problem is observed at production and quality control phases so as to prevent problems such as adhesion of the formulation to the machine parts such as the die and the punch during preparation and

possible corrosions that can arise from the friction between tablet surface and the inner wall of the die during tablet production.

As a result of the studies they conducted in line with this requirement, the inventors have found that the problems encountered at production and quality control phases during preparation of the medicaments can be solved by the formulations they have developed for preparation of dosage forms comprising quetiapine.

Description of the Invention

The present invention relates to pharmaceutical formulations comprising quetiapine and preparation methods for said formulations. Surprisingly, the inventors have seen that in the case that the formulations comprising quetiapine comprise talc, magnesium stearate, PEG 6000, silicone dioxide, sodium benzoate, potassium benzoate, stearic acid, sodium stearyl fumarate and/or a combination thereof as the lubricant, the formulation does not adhere to the punch and inner walls of the die; wear and corrosion resulting from the possible friction in said machine parts are decreased.

In this respect, the present invention relates to quetiapine formulations wherein talc, magnesium stearate, PEG 6000, silicone dioxide, sodium benzoate, potassium benzoate, stearic acid, sodium stearyl fumarate and/or a combination thereof is used as the lubricant.

In a preferred embodiment of the present invention, the lubricant used is magnesium stearate. According to the present invention, d_{100} value of magnesium stearate used is in the range of 30-250 μm, preferably in the range of 50-200 μm, more preferably in the range of 75-150 μm.

According to this, another characteristic feature of the present invention is that magnesium stearate is used as the lubricant and di_{00} value of magnesium stearate used is in the range of 30-250 μm, preferably in the range of 50-200 μm, more preferably in the range of 75-150 μm.

In other aspect, the amount of the lubricant used for preparation of the formulations comprising quetiapine is an important parameter among characteristics of the formulation to be obtained. In the case that the lubricant is used less than the required amount, this results in adhesion of the formulation prepared to the machine parts and its binding to the hollow punches. Using lubricant more than the required amount, on the other hand, causes increase in dissolution times of the dosage forms obtained. The inventors have seen that formulations are not observed to adhere to the machine parts during preparation and the dosage forms obtained

do not have long dissolution times in the case that the amount of the lubricant in the formulations comprising quetiapine is in the range of 1-20%, preferably in the range of 1-10%, and more preferably in the range of 1-5 % in proportion to total weight of the formulation. By this means, said problems encountered during both production and use of the formulations comprising quetiapine have been solved.

In another aspect, the present invention relates to formulations comprising lubricant in the range of 1-20%, preferably in the range of 1-10% and more preferably in the range of 1-5% in proportion to total weight of the formulation.

In a preferred embodiment of the present invention, the formulations comprising quetiapine are characterized in that said formulations comprise magnesium stearate in the range of 1-20%, preferably in the range of 1-10% and more preferably in the range of 1-5%.

During the studies they conducted in order to solve adhesion problem of the formulations comprising quetiapine to the machine parts, the inventors have unexpectedly found that the particle size of quetiapine and the particle size of the lubricant play a role in solving this problem effectively.

Another characteristic feature of the present invention is that the ratio of $d_{i_{00}}$ value of quetiapine to d_{100} value of the lubricant is in the range of 9:1 to 1:1, preferably in the range of 8:1 to 1:1, and more preferably in the range of 6:1 to 2:1.

- According to a preferred embodiment of the present invention, a pharmaceutical composition comprising quetiapine is characterized in that said composition comprises lubricant in the range of 1-20 %, preferably in the range of 1-10%, more preferably in the range of 1-5% and
- the ratio of d_{100} value of quetiapine to $d_{10}o$ value of the lubricant is in the range of 9:1 tol:l, preferably in the range of 8:1 to 1:1, and more preferably in the range of 6:1 to 2:1 in said composition.

According to another preferred embodiment of the present invention, the pharmaceutical composition comprising quetiapine is characterized in that

- magnesium stearate is used in the range of 1-20%, preferably in the range of 1-10%, more preferably in the range of 1-5% in said composition and

- the ratio of d_{10} value of quetiapine to d_{100} value of the lubricant is in the range of 9:1 to 1:1, preferably in the range of 8:1 to 1:1 and more preferably in the range of 6:1 to 2:1.

Percentage values of amounts given in scope of the present invention are calculated in proportion to unit dosage weight.

Quetiapine comprised in the pharmaceutical formulations of the present invention can be in form of its pharmaceutically acceptable salts, hydrates, solvates, esters, enantiomers, diastereomers or combinations thereof in terms of chemical structure; in crystalline, amorphous forms or combinations thereof in terms of polymorphic structure. Quetiapine is preferably in quetiapine fumarate form.

The pharmaceutical formulations of the present invention comprising quetiapine and lubricant can be prepared in any dosage form 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.

The pharmaceutical formulations of the present invention comprising quetiapine and lubricant are preferably in powder, tablet and granule forms, more preferably in form of tablet, film tablet or effervescent tablet.

In another aspect, the present invention relates to the pharmaceutical formulations comprising quetiapine and lubricant in form of tablet, film tablet or effervescent tablet.

The pharmaceutical formulation obtained can be formed into any abovementioned dosage forms. In the case that the formulation is in tablet form, the tablets obtained can be treated with film coating agents, for instance sugar based coating agents, water soluble film coating agents, enteric coating agents, delayed release coating agents or coating compositions comprising any combination thereof.

Saccharose can be used singly or optionally with any of the agents such as talc, calcium carbonate, calcium phosphate, calcium sulphate, gelatine, gum arabic, polyvinylpyrrolidone and pullulan or any combination thereof as the sugar based coating agent.

The water soluble film coating agent can be selected from cellulose derivatives such as hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, methyl hydroxyethyl cellulose and sodium carboxymethyl cellulose; synthetic polymers such as

polyvinyl acetal diethyl aminoacetate, aminoalkyl methacrylate copolymers and polyvinylpyrrolidone and polysaccharides such as pullulan or combinations thereof.

The enteric coating agents can be selected from cellulose derivatives such as hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, carboxymethyl ethyl cellulose, cellulose acetate phthalate; acrylic acid derivatives such as methacrylic acid copolymer L, methacrylic acid copolymer LD and methacrylic acid copolymer S and natural substances such as shellac or combinations thereof.

The delayed release coating agents can be selected from cellulose derivatives such as ethyl cellulose; acrylic acid derivatives such as aminoalkyl methacrylate copolymer RS, emulsion copolymer of ethyl acrylate-methyl methacrylate or combinations thereof.

The pharmaceutical formulations of the present invention comprising quetiapine and lubricant can comprise various excipients in addition to the active agent quetiapine and the lubricant.

The pharmaceutical formulations of the present invention comprising quetiapine and lubricant comprise at least one excipient selected from a group comprising disintegrant, diluent, glidant, binder, optionally effervescent couple comprising at least one acidic agent and at least one basic agent, coloring agent, pH regulating agent, surfactant, stabilizing agent, sweetener and/or taste regulating agent, flavoring agent, antiadherant in addition to the active agent quetiapine and the lubricant.

The disintegrant that can be used in the pharmaceutical formulations of the present invention comprising quetiapine and lubricant 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.

The diluent that can be used in the pharmaceutical formulations of the present invention comprising quetiapine and lubricant 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, sodium chloride, sucrose, talc, xylitol.

The glidant that can be used in the pharmaceutical formulations of the present invention comprising quetiapine and lubricant can be selected from a group comprising tribasic calcium phosphate, colloidal silicone dioxide, magnesium silicate, magnesium trisilicate, talc.

The binder that can be used in the pharmaceutical formulations of the present invention comprising quetiapine and lubricant 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.

The inventors have seen that using more than one binders in the formulation has an influence on the dissolution time of the resulting dosage form. It has been observed that when a binder combination comprising at least two binders is used, the obtained dosage form can be dissolved rapidly, thus a high absorption of the drug and an effective treatment can be provided.

In another aspect, the present invention relates to the pharmaceutical formulations comprising quetiapine wherein said formulation comprises a binder combination comprising at least two binders.

Moreover, it has been also observed that in the case that the ratio of the first binder to the second binder is in the range of 25:1 to 1:1, preferably 20:1 to 2:1, more preferably 15:1 to 3:1 by weight, the obtained dosage form can dissolve rapidly resulting in a high absoption of quetiapine active agent.

In another aspect, the present invention relates to the pharmaceutical formulations comprising quetiapine wherein said formulation comprises a binder combination comprising first and second binder and wherein the ratio of the first binder to the second binder is in the range of 25:1 to 1:1, preferably 20:1 to 2:1, more preferably 15:1 to 3:1 by weight.

In a preferred embodiment of the present invention, the first binder is starch.

In a preferred embodiment of the present invention, the second binder is povidone.

In another aspect, the present invention relates to the pharmaceutical formulations comprising quetiapine wherein said formulation comprises a binder combination comprising starch and povidone and wherein the ratio of starch to povidone is in the range of 25:1 to 1:1, preferably 20:1 to 2:1, more preferably 15:1 to 3:1 by weight.

In another aspect, the present invention relates to the pharmaceutical formulations comprising quetiapine wherein said formulation comprises a binder combination in an amount in the range of 5-40%, preferably 10-30% in proportion to the total weight of the pharmaceutical formulation.

The acidic agent composing the effervescent couple comprising at least one acidic agent and at least one basic agent that can be used in the pharmaceutical formulations of the present invention comprising quetiapine and lubricant can be selected from a group comprising organic acids such as malic acid, citric acid, tartaric acid, fumaric acid; and the basic agent can be selected from a group comprising agents such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate.

The pH regulating agent that can be used in the pharmaceutical formulations of the present invention comprising quetiapine and lubricant can be selected from citrate, phosphate, carbonate, tartrate, fumarate, acetate and amino acid salts.

The surfactant that can be used in the pharmaceutical formulations of the present invention comprising quetiapine and lubricant can be selected from sodium lauryl sulphate, polysorbate, polyoxyethylene, polyoxypropylene glycol and similar agents.

The stabilizing agent that can be used in the pharmaceutical formulations of the present invention comprising quetiapine and lubricant can be selected from a group comprising tocopherol, tetrasodium edetate, nicotinamide, cyclodextrin.

The sweetener and/or taste regulating agent that can be used in the pharmaceutical formulations of the present invention comprising quetiapine and lubricant 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.

The flavoring agent that can be used in the pharmaceutical formulations of the present invention comprising quetiapine and lubricant can be selected from flavors comprising menthol, lemon, orange, vanilla, strawberry, raspberry, caramel and similar flavors.

The antiadherant that can be used in the pharmaceutical formulations of the present invention can be selected from talc, starch, colloidal silica, L-leucine and sodium sulfate.

According to a preferred embodiment of the present invention, the pharmaceutical composition comprising quetiapine is characterized in that

- the lubricant is used in the range of 1-20%, preferably in the range of 1-10%, more preferably in the range of 1-5 % in said composition and
- the ratio of d_{100} value of quetiapine to d_{100} value of the lubricant is in the range of 9:1 to 1:1, preferably in the range of 8:1 to 1:1 and more preferably in the range of 6:1 to 2:1 in said composition
- said composition comprises at least one excipient selected from a group comprising disintegrant, diluent, glidant, binder, optionally effervescent couple comprising at least one acidic agent and at least one basic agent, coloring agent, pH regulating agent, surfactant, stabilizing agent, sweetener and/or taste regulating agent, flavoring agent, antiadherant in addition to quetiapine and the lubricant.

In another preferred embodiment of the present invention, the pharmaceutical composition comprising quetiapine is characterized in that

- magnesium stearate is used in the range of 1-20%, preferably in the range of 1-10%, more preferably in the range of 1-5% in said composition and
- the ratio of d_{100} value of quetiapine to d_{100} value of magnesium stearate is in the range of 9:1 to 1:1, preferably in the range of 8:1 to 1:1 and more preferably in the range of 6:1 to 2:1 in said composition.

The pharmaceutical formulation of the present invention comprises at least one excipient selected from a group comprising disintegrant, diluent, glidant, binder, effervescent couple comprising at least one acidic agent and at least one basic agent, coloring agent, pH regulating agent, surfactant, stabilizing agent, sweetener and/or taste regulating agent, flavoring agent in addition to quetiapine and magnesium stearate.

The pharmaceutical formulations of the present invention comprising quetiapine and lubricant can comprise quetiapine in the range of 0.1 to 99 % by weight, preferably in the range of 1 to 97 % by weight, more preferably in the range of 5 to 95% by weight.

The pharmaceutical formulations of the present invention can comprise quetiapine in the range of 5 to 95%, lubricant in the range of 1-5% disintegrant in the range of 1-10%, diluent in the range of 5-30%, binder in the range of 10-30%, glidant in the range of 0.1-3%, antiadherant in the range of 0.2-5% in proportion to total weight of the formulation.

The pharmaceutical formulations of the present invention comprising quetiapine and lubricant can optionally comprise a second active agent in addition to quetiapine. The second active agent can be selected from antacid, anticholinergic, antispasmodic, antiemetic, antidiabetic, antipropulsive, antiallergic, antidiarrheal, antiobesity, antithrombotic, antifibrinolytic, antianemic, antihypertensive, antifungal, antipruritic, antipsoriatic, antibiotic, antiseptic, antiacne, antibacterial, antimycotic, antiviral, antineoplastic, antiarrhythmic, antiadrenergic, antiepileptic, anti-parkinson, antiprotozoal, anthelmintic, anti-inflammatory, diuretic, laxative, sulphonamide, imidazole, corticosteroid, thiazolidinedione, biguanide, immunostimulant, immunosuppressant, myorelaxant, analgesic, psycholeptic, psychoanaleptic peripheral vasodilator, beta blocker, calcium channel blocker and lipid modifying agents; alpha-glucosidase inhibitors, aldose reductase inhibitors, ACE inhibitors; multivitamin and minerals, vitamin A, vitamin D and its analogues, vitamin B_1, vitamin C, vitamin E, vitamin B_6, vitamin B_2, vitamin K, calcium, potassium, sodium, zinc, magnesium, fluoride, selenium.

The pharmaceutical formulation of the present invention can be obtained by a method comprising the steps of

- stirring the active agent quetiapine and, if available, the second active agent homogeneously; if required, adding at least one of the abovementioned excipients and the lubricant or
- stirring the active agent quetiapine and, if available, the second active agent homogeneously after granulated with at least one of the excipients and adding the lubricant or
- stirring the active agent quetiapine and, if available, the second active agent with at least one of the excipients and at least one of the abovementioned excipients; optionally granulating them with the granulation solution comprising excipient and stirring the granules obtained with the lubricant and optionally at least one excipient or
- using any of the abovementioned methods separately for the active agent compositions and then combining the formulations obtained in the case that two active agents are used.

The pharmaceutical formulation of the present invention can be used in treatment of schizophrenia, depressive episodes related to bipolar disorder, acute manic episodes related to bipolar disorder and in continuous treatment of bipolar disorders.

EXAMPLE: Film coated tablets comprising quetiapine and their preparation methods

Component name	% of amount in unit dose
Quetiapine fumarate	45 %
Magnesium stearate	1.25 %
Other excipients	53.75 %
Film coating agent	3 %

In obtainment of the formulation that shall be used in the present invention, quetiapine fumarate is mixed with the other excipients. Magnesium stearate is added into this mixture as the lubricant and the final mixture is compressed in tablet form. The tablets are optionally coated with film coating solution.

CLAIMS

1. A pharmaceutical formulation comprising quetiapine, characterized in that said formulation comprises talc, magnesium stearate, PEG 6000, silicone dioxide, sodium benzoate, potassium benzoate, stearic acid, sodium stearyl fumarate and/or a combination thereof as the lubricant.
2. The pharmaceutical formulation comprising quetiapine according to claim 1, characterized in that the amount of the lubricant is in the range of 1-20% in proportion to total amount of the formulation.
3. The pharmaceutical formulation comprising quetiapine according to claim 2, characterized in that the amount of the lubricant is in the range of 1-10% in proportion to total amount of the formulation.
4. The pharmaceutical formulation comprising quetiapine according to claim 3, characterized in that the amount of the lubricant is in the range of 1-5% in proportion to total amount of the formulation.
5. The pharmaceutical formulation comprising quetiapine according to any preceding claims, wherein magnesium stearate is used as the lubricant.
6. The pharmaceutical formulation comprising quetiapine according to any preceding claims, wherein the ratio of d_{100} value of quetiapine to $\mathbf{d_{100}}$ value of the lubricant is in the range of 9:1 to 1:1.
7. The pharmaceutical formulation comprising quetiapine according to any preceding claims, wherein the ratio of $\mathbf{d_{100}}$ value of quetiapine to d_{100} value of the lubricant is in the range of 8:1 to 1:1.
8. The pharmaceutical formulation comprising quetiapine according to any preceding claims, wherein the ratio of $\mathbf{d_{100}}$ value of quetiapine to di_{00} value of the lubricant is in the range of 6:1 to 2:1.
9. The pharmaceutical formulation comprising quetiapine according to any preceding claims, wherein said formulation is prepared in any of the dosage forms of 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.
10. The pharmaceutical formulation comprising quetiapine according to claim 9, wherein said formulation is in tablet, film tablet or effervescent tablet forms.

11. The pharmaceutical formulation comprising quetiapine according to any preceding claims, wherein quetiapine is in the form of its pharmaceutically acceptable derivatives; salts, hydrates, solvates, esters, enantiomers, disastereomers or combinations thereof in terms of chemical structure.

12. The pharmaceutical formulation comprising quetiapine according to claim 11, wherein quetiapine is in pharmaceutically acceptable quetiapine fumarate form.

13. The pharmaceutical formulation comprising quetiapine according to any preceding claims, wherein quetiapine is in amorphous form or crystalline form or a combination thereof in terms of polymorphic structure.

14. The pharmaceutical formulation comprising quetiapine according to any preceding claims, wherein said formulation comprises pharmaceutically acceptable excipients along with quetiapine and the lubricant.

15. The pharmaceutical formulation comprising quetiapine according to claim 14, wherein said formulation comprises at least one excipient selected from a group comprising disintegrant, diluent, glidant, binder, effervescent couple comprising at least one acidic agent and at least one basic agent, coloring agent, pH regulating agent, surfactant, stabilizing agent, sweetener and/or taste regulating agent, flavoring agent, antiadherant in addition to quetiapine and the lubricant.

16. The pharmaceutical formulation comprising quetiapine according to claim 15, wherein said formulation comprises a binder combination comprising at least two binders.

17. The pharmaceutical formulation comprising quetiapine according to claim 16, wherein said formulation comprises a binder combination comprising first and second binder and wherein the ratio of the first binder to the second binder is in the range of 25:1 to 1:1 by weight.

18. The pharmaceutical formulation comprising quetiapine according to claims 16 and 17, wherein said formulation comprises a binder combination comprising first and second binder and wherein the ratio of the first binder to the second binder is in the range of 20:1 to 2:1 by weight.

19. The pharmaceutical formulation comprising quetiapine according to claim 18, wherein said formulation comprises a binder combination comprising first and second binder and wherein the ratio of the first binder to the second binder is in the range of 15:1 to 3:1 by weight.

20. The pharmaceutical formulation comprising quetiapine according to claim 16-19, wherein said formulation comprises a binder combination comprising first and second binder and wherein the first binder is starch and the second binder is povidone.
21. The pharmaceutical formulation comprising quetiapine according to claim 16-20, wherein the ratio of starch to povidone is in the range of 25:1 to 1:1 by weight.
22. The pharmaceutical formulation comprising quetiapine according to any preceding claims, wherein said formulation comprises the active agent quetiapine in the range of 0.1 to 99% by weight.
23. The pharmaceutical formulation comprising quetiapine according to claim 22, wherein said formulation comprises the active agent quetiapine in the range of 1 to 97% by weight.
24. The pharmaceutical formulation comprising quetiapine according to claims 21 and 23, wherein said formulation comprises the active agent quetiapine in the range of 5 to 95% by weight.
25. The pharmaceutical formulation comprising quetiapine according to any preceding claims, wherein said formulation comprises quetiapine in the range of 5 to 95%, lubricant in the range of 1-5%, disintegrant in the range of 1-10%, diluent in the range of 5-30%, binder in the range of 10-30%, glidant in the range of 0.1-3%, antiadherant in the range of 0.2-5% in proportion to total weight of the formulation.
26. The pharmaceutical formulation comprising quetiapine according to any preceding claims, wherein said formulation comprises at least a second active agent in addition to quetiapine selected from antacid, anticholinergic, antispasmodic, antiemetic, antidiabetic, antipropulsive, antiallergic, antidiarrheal, antiobesity, antithrombotic, antifibrinolytic, antianemic, antihypertensive, antifungal, antipruritic, antipsoriatic, antibiotic, antiseptic, antiacne, antibacterial, antimycotic, antiviral, antineoplastic, antiarrhythmic, antiadrenergic, antiepileptic, anti-parkinson, antiprotozoal, anthelmintic, anti-inflammatory, diuretic, laxative, sulphonamide, imidazole, corticosteroid, thiazolidinedione, biguanide, immunostimulant, immunosuppressant, myorelaxant, analgesic, psycholeptic, psychoanaleptic peripheral vasodilator, beta blocker, calcium channel blocker and lipid modifying agents; alpha-glucosidase inhibitors, aldose reductase inhibitors, ACE inhibitors; multivitamin and minerals, vitamin A, vitamin D and its analogs, vitamin B_1, vitamin C, vitamin E, vitamin B_6, vitamin B_2, vitamin K, calcium, potassium, sodium, zinc, magnesium, fluoride, selenium.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2012/000235

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/554
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 , CHEM ABS Data, EMBASE, WPI Data, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/244093 Al (BOEHM GARTH [US] ET AL) 18 October 2007 (2007-10-18) exampl es page 7, paragraph 0085	1-26
X	EP 2 153 834 A2 (FARMAPROJECTS S A [ES]) 17 February 2010 (2010-02-17) exampl es	1-26
X	DE 10 2008 046650 Al (TI EFENBACHER PHARMACHEMI KALI EN [DE]) 11 March 2010 (2010-03-11) exampl es page 4, paragraph 0031	1-26

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
2 Apri l 2013	09/04/2013

Name and mailing address of the ISA/	Authorized officer
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1

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2012/000235

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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