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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 January 2012 (12.01.2012)

PCT

(10) International Publication Number
WO 2012/005709 A2

(51) **International Patent Classification:**
A61K 9/16 (2006.01)

(21) **International Application Number:**
PCT/TR201 1/000168

(22) **International Filing Date:**
4 July 201 1 (04.07.201 1)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
2010/05419 5 July 2010 (05.07.2010) 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, 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, PE, PG, PH, PL, PT, RO, RS, RU, 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, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, 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:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2012/005709 A2

(54) **Title:** PHARMACEUTICAL COMPOSITION COMPRISING VALSARTAN

(57) **Abstract:** The present invention relates to a pharmaceutical composition composed of granules comprising valsartan and optionally pharmaceutically acceptable excipients.

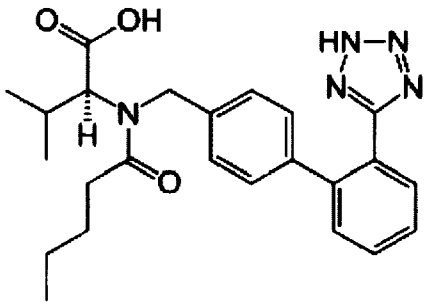
PHARMACEUTICAL COMPOSITION COMPRISING VALSARTAN

Purpose of the Invention

The present invention relates to a pharmaceutical composition composed of granules comprising valsartan and optionally pharmaceutically acceptable excipients.

Background of the Invention

Valsartan (Formula I), which was disclosed in the patent numbered EP0443983 (Bl) for the first time, is named (5)-3-methyl-2-*[N*-({4-[2-(2*H*-l,2,3,4-tetrazol-5-yl)phenyl]phenyl }methyl)pentanamido]butanoic acid.



Formula 1

The medicaments DIOVAN and CARDOPAN are two examples of the drugs comprising the active agent valsartan used in diseases such as hypertension and coronary failure. These drugs are in film coated tablet form.

When valsartan contacts with air, it absorbs the water vapor in the air due to its crystalline structure. This causes the pharmaceutical composition comprising it to contain moisture. Pharmaceutical compositions with high moisture hold problems such as adhesion, staining. Furthermore, high moisture leads to degradation of the active agents and excipients and hence affects the stability of the pharmaceutical composition negatively.

Many studies have been conducted in order to solve the moisture problem in the prior art. In the patent application numbered WO2009022169, a formulation prepared by wet granulation method in which valsartan contains less than 3% moisture was disclosed. In addition, valsartan formulations containing no moisture were also disclosed in this patent. However, many problems are encountered in pharmaceutical compositions which are very dry or contain no moisture. One of these problems is that some part of the outer part of the tablet is

broken apart from the main part of the tablet in the course of compression. Another similar problem is that the tablet horizontally breaks into two or more pieces. Furthermore, it is also possible that edges of the tablet breaks into pieces since the tablet is dry.

In the present day, there is need for new formulations in which the problems specified above are minimized or prevented.

Detailed Description of the Invention

The inventor has surprisingly found that the pharmaceutical composition prepared with granules comprising valsartan in which the moisture rate is in the range of 3% to 10% minimizes or prevents the problems specified above.

The present invention provides a pharmaceutical composition that is composed of granules comprising valsartan and optionally pharmaceutically acceptable excipients in which the moisture rate of said granules is adjusted in the range of 3% to 10%.

The present invention provides a pharmaceutical composition comprising valsartan granules which optionally contain pharmaceutically acceptable excipients and/or pharmaceutically acceptable active agents.

In another aspect, the present invention provides a process developed in order to keep the moisture rate of the granules in the range of 3% to 10%. According to said process; after valsartan, optionally one or more pharmaceutically acceptable excipients and/or optionally one or more pharmaceutically acceptable active agents are granulated with a suitable granulation solution, they are taken to the fluid bed dryer and dried at 50°C. Thus, the pharmaceutical composition is ensured to be stable by reducing the moisture rate. Furthermore, the tablet is impeded to break into pieces or a layer to break apart from the main part of the tablet during compression or coating since the moisture rate of the pharmaceutical composition is not less than 3%.

According to the present invention, the granulation solution used in preparation of the granules can be selected from a group comprising solvents such as water, deionized water, toluene, benzene, acetone, methyl acetate, tetrahydrofuran, heptane, hexane, acetonitrile, alcohol (e.g. ethyl alcohol) and/or alcohol mixture though it can preferably be ethyl alcohol and/or deionized water. According to this, with the present invention, valsartan granules

prepared with the granulation solution comprising ethyl alcohol and deionized water are dried and their moisture rate is ensured to be in the range of 3% to 10%.

According to the present invention, "valsartan" also refers to pharmaceutically acceptable derivatives of valsartan. Pharmaceutically acceptable derivatives of valsartan comprise its pharmaceutically acceptable solvates, hydrates, enantiomers or diastereomers, racemates, free base, organic salts, inorganic salts, esters, polymorphs, crystalline forms and amorphous forms and/or combinations thereof.

According to another aspect of the present invention, the pharmaceutically acceptable excipient used in the pharmaceutical composition can be selected from a group comprising diluents, binders, disintegrants, glidant, alkalinizing agents, lubricants, coating agents and/or combinations thereof. In addition to these, the pharmaceutical composition can further comprise other excipients such as solvents, electrolytes and coloring agents.

The present invention provides a medicament in which the excipients are selected from a group comprising diluents such as calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium lactate, tribasic calcium sulfate cellulose, microcrystalline cellulose, siliconized microcrystalline cellulose, cellulose powder, dextrate, dextrin, dextrose, fructose, kaolin, lactitol, lactose, maltose, mannitol, sorbitol, starch, pregelatinized starch, pregelatinized sucrose, compressible sugar and/or combinations thereof; and in which these diluents are preferably mannitol, microcrystalline cellulose and/or lactose.

The present invention provides a medicament in which the excipients are selected from a group comprising binders such as starch, pregelatinized starch, pregelatinized syrup, alginic acid, carboxymethyl cellulose, sodium cellulose, microcrystalline dextrin ethyl cellulose gelatin glucose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxyproyl cellulose, low-substituted hydroxypropyl cellulose, polyvinylpyrrolidone, crospovidone, polymethacrylate and/or combinations thereof; and in which these binders are preferably crospovidone, starch, pregelatinized starch and/or microcrystalline cellulose.

The present invention provides a medicament in which the excipients are selected from a group comprising disintegrants such as alginic acid cellulose, microcrystalline croscarmellose sodium, carboxymethyl cellulose sodium, crospovidone, polacrylline potassium, sodium starch glicolate, starch, pregelatinized starch and/or combinations thereof; and in which these disintegrants are preferably crospovidone and/or microcrystalline cellulose.

The present invention provides a medicament comprising valsartan and/or pharmaceutically acceptable derivatives thereof and excipients in which the excipients are selected from a group comprising glidants such as calcium silicate, magnesium silicate, magnesium trisilicate, tribasic calcium phosphate, metallic stearates, metallic lauryl sulfates, silicone dioxide, colloidal talc, colloidal silicone dioxide, microcrystalline cellulose and/or combinations thereof; and in which these glidants are preferably silicone dioxide.

The present invention provides a medicament in which the excipients are selected from a group comprising alkalinizing agents such as alkali metal salts such as sodium carbonate, sodium hydroxide, sodium silicate, disodium hydrogen orthophosphate, sodium aluminate; alkaline earth metal salts such as calcium carbonate, calcium hydroxide, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, calcium acetate, calcium gluconate, calcium glycerophosphate, magnesium carbonate, magnesium hydroxide, magnesium sulphate, magnesium acetate, magnesium silicate, magnesium aluminate; and organic compounds such as primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzylethylenediamine, diethanolamine, ethylenediamine, meglumine, monosodium glutamate, polacryline sodium, sodium alginate and/or combinations thereof; and in which these alkalinizing agents are preferably sodium hydrogen carbonate.

The present invention provides a medicament in which the excipients are selected from a group comprising lubricants such as calcium stearate, glyceryl behenate, magnesium stearate, calcium stearate, mineral oil, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, vegetable oil, fatty acid esters, paraffins, leucine, hydrogenated vegetable oils, metallic lauryl sulfate, sodium chloride sodium benzoate, sodium acetate and/or combinations thereof; and in which the lubricant is preferably magnesium stearate.

The present invention provides a medicament in which the excipients are selected from a group comprising coating agents such as carboxymethyl cellulose, sodium cellulose acetate phthalate, ethylcellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl methyl cellulose phthalate, methacrylic acid copolymer, methylcellulose polyethylene glycol, polyvinyl acetate, titanium dioxide, wax, carnauba wax and/or combinations thereof; and in which these coating agents are preferably hydroxyl propyl methyl cellulose, titanium dioxide and/or polyethylene glycol.

The present invention provides a pharmaceutical composition comprising

a. valsartan in the range of 10% to 34% by weight and preferably in the range of 25% to 34% by weight;
b. diluent in the range of 30% to 65% by weight and preferably in the range of 45% to 60% by weight;
c. disintegrant in the range of 1% to 15% by weight and preferably in the range of 1% to 10% by weight;
d. glidant in the range of 0% to 10% by weight and preferably in the range 0,1% to 5% by weight;
e. alkalinizing agent in the range of 0% to 15% by weight and preferably in the range of \% to 10% by weight;
f. lubricant in the range of 0% to 10% by weight and preferably in the range of 0,1% to 5% by weight.

According to the present invention in another aspect, the pharmaceutical composition can be in coated or uncoated tablet, orally disintegrated tablet, capsule, pellet, powder, granule or mini tablet form and preferably in coated tablet form.

According to the present invention in another aspect, the pharmaceutical composition can be prepared by conventional methods after the granulation and drying operations of the present invention are applied.

According to the present invention in another aspect, the pharmaceutical composition can additionally comprise one or more excipients selected from a group comprising rennin inhibitor, angiotensin converting enzyme inhibitor, calcium channel blocker, aldosterone synthesis inhibitor, aldosterone antagonist, endothelin antagonist and diuretic.

According to the present invention, the pharmaceutical composition can additionally comprise one or more active agents selected from a group comprising aliskiren, remikiren, captopril, zofenopril, enalapril, ramipril, quinapril, perindopril, lisinopril, benazepril, fosinopril, alacepril, cilazapril, delapril, imidapril, moexipril, rentiapril, spinapril, temocapril, trandolapril; dihydropyridines such as amlodipine, nifedipine, nilvadipine, nicardipine; verapamil, gallopamil, diltiazem, fendiline, mibefradil, bepridil, fluspirilene, spironolactone, eplerenone, canrenone, prorenone, mexrenone, hydrochlorothiazide, trichlormethiazide, epitizide, altizide, mebutizide, chlortalidone, cyclopenthiazide, metolazone, bendroflumethiazide, butizide, furosemide, bumetanide, conivaptan, mozavaptan, satavaptan, tolvaptan, theobromine, cicletanine and/or combinations thereof. These active agents

additionally added to the pharmaceutical composition of the present invention can preferably be amlodipine and/or hydrochlorothiazide.

In another aspect, the present invention relates to use of the pharmaceutical composition in the treatment or prophylaxis of, as preferably hypertension, congestive heart failure, angina, myocardial infarction, embolism, diabetic nephropathy, diabetic cardiomyopathy, renal failure, peripheral vascular diseases, left ventricular hypertrophy, cognitive dysfunction, Alzheimer disease, paralysis, headache and chronic heart disease.

Content of the pharmaceutical composition according to the present invention can be explained by the examples below, yet cannot be limited to these examples.

FORMULATION EXAMPLES:

EXAMPLE 1:

Content	**Amount**
Valsartan	80 mg
Diluent	140 mg
Disintegrant	12 mg
Glidant	1 mg
Alkalinizing agent	13 mg
Lubricant	4 mg
Total Amount	250 mg
Moisture Rate of Granules	%3,5

EXAMPLE 2:

Content:	**Amount**
Valsartan	80 mg
Diluent	150 mg
Disintegrant	13 mg
Glidant	1 mg
Alkalinizing agent	10 mg
Lubricant	5 mg
Total Amount	260 mg
Moisture Rate of Granules	%4

EXAMLE 3:

Content:	**Amount**
Valsartan	80 mg
Diluent	140 mg
Disintegrant	10 mg
Glidant	1 mg
Alkalinizing agent	12 mg
Lubricant	5 mg
Total Amount	250 mg
Moisture Rate of Granules	%3,5

PROCESS EXAMPLES OF GRANULES:

EXAMPLE 4:

A granulation solution is prepared by mixing a suitable amount of ethyl alcohol and deionized water. The active agent valsartan of 80 mg is mixed with the granulation solution prepared and it is granulated. The granules are taken to the fluid bed dryer. They are dried at 50°C there and valsartan granules with 3,5% moisture content are obtained.

Claims:

1. A pharmaceutical composition comprising valsartan granules and optionally pharmaceutically acceptable excipients characterized in that the moisture rate of said granules is in the range of 3% to 10%.
2. The pharmaceutical composition according to claim 1, wherein the granules in said composition can comprise pharmaceutically acceptable excipients and/or optionally pharmaceutically acceptable active agents.
3. The pharmaceutical composition according to claim 1, wherein the granules in said composition are obtained by a process comprising the steps of;
    a. granulating valsartan with a suitable granulation solution;
    b. taking the granules obtained to fluid bed dryer;
    c. drying the granules at 50°C such that the moisture rate of the granules is in the range of 3% to 10%.
4. The pharmaceutical composition according to claim 3, wherein the granulation solution can comprise one or more pharmaceutically acceptable excipients.
5. The pharmaceutical composition according to any one of the preceding claims, wherein the pharmaceutically acceptable excipient used can be selected from a group comprising solvents, diluents, binders, disintegrants, glidants, alkalinizing agents, lubricants and/or combinations thereof.
6. The pharmaceutical composition according to claim 5, wherein the solvent can be selected from a group comprising water, deionized water, toluene, benzene, acetone, methyl acetate, tetrahydrofuran, heptane, hexane, acetonitrile, alcohol (e.g. ethyl alcohol) and/or combinations thereof.
7. The pharmaceutical composition according to claim 6, wherein the excipient solvent is ethyl alcohol and/or deionized water.
8. The pharmaceutical composition according to claim 5, wherein the excipient diluent can be selected from a group comprising calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium lactate, tribasic calcium sulfate cellulose, microcrystalline cellulose, siliconized microcrystalline cellulose, cellulose powder, dextrate, dextrin, dextrose, fructose, kaolin, lactitol, lactose, maltose, mannitol, sorbitol, starch, pregelatinized starch, pregelatinized sucrose, compressible sugar and/or combinations thereof.

9. The pharmaceutical composition according to claim 5, wherein the excipient binder can be selected from a group comprising starch, pregelatinized starch, pregelatinized syrup, alginic acid, carboxymethyl cellulose, sodium cellulose, microcrystalline dextrin ethyl cellulose gelatin glucose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxyproyl cellulose, low-substituted hydroxypropyl cellulose, polyvinylpyrrolidone, crospovidone, polymethacrylate and/or combinations thereof.
10. The pharmaceutical composition according to claim 5, wherein the excipient disintegrant can be selected from a group comprising alginic acid cellulose, microcrystalline croscarmellose sodium, carboxymethyl cellulose sodium, crospovidone, polacrylline potassium, sodium starch glicolate, starch, pregelatinized starch and/or combinations thereof.
11. The pharmaceutical composition according to claim 5, wherein the excipient glidant can be selected from a group comprising calcium silicate, magnesium silicate, magnesium trisilicate, tribasic calcium phosphate, metallic stearates, metallic lauryl sulfates, silicone dioxide, colloidal talc, colloidal silicone dioxide, microcrystalline cellulose and/or combinations thereof.
12. The pharmaceutical composition according to claim 5, wherein the excipient alkalinizing agent can be selected from a group comprising alkali metal salts such as sodium carbonate, sodium hydroxide, sodium silicate, disodium hydrogen orthophosphate, sodium aluminate; alkaline earth metal salts such as calcium carbonate, calcium hydroxide, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, calcium acetate, calcium gluconate, calcium glycerophosphate, magnesium carbonate, magnesium hydroxide, magnesium sulphate, magnesium acetate, magnesium silicate, magnesium aluminate; and organic compounds such as primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzylethylenediamine, diethanolamine, ethylenediamine, meglumine, monosodium glutamate, polacryline sodium, sodium alginate and/or combinations thereof.
13. The pharmaceutical composition according to claim 5, wherein the excipient lubricant can be selected from a group comprising calcium stearate, glyceryl behenate, magnesium stearate, calcium stearate, mineral oil, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, vegetable oil, fatty acid esters, paraffins, leucine, hydrogenated vegetable oils, metallic lauryl sulfate, sodium chloride sodium benzoate, sodium acetate and/or combinations thereof.

14. The pharmaceutical composition according to any one of the preceding claims, wherein the pharmaceutically acceptable active agent used can be selected from a group comprising rennin inhibitor, angiotensin converting enzyme inhibitor, calcium channel blocker, aldosterone synthesis inhibitor, aldosterone antagonist, endothelin antagonist and diuretic and/or combinations thereof.
15. The pharmaceutical composition according to claim 14, wherein the pharmaceutically acceptable active agent in said composition can be one or more calcium channel blockers and/or diuretics.
16. The pharmaceutical composition according to claim 15, wherein the calcium channel blocker can be amlodipine.
17. The pharmaceutical composition according to claim 16, wherein the diuretic substance can be hydrochlorothiazide.