

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
9 February 2006 (09.02.2006)

PCT

(10) International Publication Number
WO 2006/013545 A1

(51) International Patent Classification:

A61K 31/415 (2006.01) A61K 9/20 (2006.01)
A61K 31/54 (2006.01)

(21) International Application Number:

PCT/IB2005/052549

(22) International Filing Date: 28 July 2005 (28.07.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

1396/Del/2004 28 July 2004 (28.07.2004) IN

(71) Applicant (for all designated States except US): **RAN-BAXY LABORATORIES LIMITED** [IN/IN]; Plot No. 90, Sector - 32, Gurgaon, Haryana 122 001 (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MURPANI, Deepak** [IN/IN]; C-213, Lajpat Nagar, Part - I, New Delhi, Delhi 110024 (IN). **RAHEJA, Praveen** [IN/IN]; C-1A/3B, Janak Puri, New Delhi, Delhi 110058 (IN). **KUMAR, Shanmugam** [IN/IN]; No. 16/10A, Pillaiyar Kiol Street, Anumanthaputheri, Chengalpattu, Chengai Anna, Tamil Nadu 603002 (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jay R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICAL COMPOSITIONS OF IRBESARTAN

(57) Abstract: The present invention relates to pharmaceutical compositions comprising irbesartan and hydrochlorothiazide and processes for the preparation thereof.



WO 2006/013545 A1

Description

PHARMACEUTICAL COMPOSITIONS OF IRBESARTAN

Technical Field

- [1] The present invention relates to pharmaceutical compositions comprising irbesartan and hydrochlorothiazide and processes for the preparation thereof.

Background Art

- [2] When given as monotherapy, antihypertensive drugs normalize blood pressure in only a fraction of hypertensive patients. Treatment with two or more agents from different pharmacological classes is often necessary to achieve adequate blood pressure control. The rationale for using combination therapy is to obtain increased blood pressure control by employing two antihypertensive agents with different modes of action and to enhance compliance by using a single tablet that is taken once or twice daily.
- [3] Fixed dose combinations that include angiotensin-receptor blockers (AT1-receptor blocker) and diuretics are very effective in controlling blood pressure in cases where monotherapy fails to provide adequate control. The administration of diuretics alone results in sodium depletion and a compensatory rise in renin secretion. A simultaneous blockade of the renin-angiotensin system, with an AT1-receptor blocker, makes this compensatory hyper-reninemia ineffective and allows for the maximum benefit from sodium depletion.
- [4] Irbesartan, a long-acting angiotensin-II receptor antagonist, is useful in the treatment of various cardiovascular ailments including hypertension and heart failure. Sanofi Synthelabo markets a combination of irbesartan and hydrochlorothiazide as oral tablets under the brand name AVALIDE®. These tablets comprise two different strengths of irbesartan (150 mg and 300 mg) and one strength of hydrochlorothiazide (12.5 mg). The average weight of the tablet comprising 300 mg irbesartan and 12.5 mg hydrochlorothiazide is 600 mg and the average weight of the tablet comprising 150 mg irbesartan and 12.5 mg hydrochlorothiazide is 300 mg. These tablets have an irbesartan content of approximately 50% based on the tablet weight, which indicates that the tablets are large and contain a large proportion of excipients.
- [5] U.S. Patent No. 5,994,348 discloses that the physical properties of irbesartan and hydrochlorothiazide present difficulties in developing formulations suitable for preparing a tablet having both a substantial quantity of active agent and a small size to allow for easy swallowing. Both irbesartan and hydrochlorothiazide are fluffy materials with low densities, poor flow characteristics, a resistance to blending and dispersion in liquids due to agglomeration and poor wetting qualities. These powders are also likely to exhibit static charge effects. Irbesartan also exhibits poor aqueous

solubility and has a tendency to stick to the punches and dies used in the tableting procedure.

- [6] These properties of the active ingredients render the task of developing a pharmaceutical composition difficult and laborious. Improved tableting and flow characteristics may be achieved through addition of those excipients that can increase cohesiveness, decrease sticking and provide bulk to the powder or the granulate. However, for high dose actives the total amount of excipients added has to be kept at a minimum so as to keep the size of the dosage form comfortable enough to be swallowed.
- [7] Therefore, there is a need in the art for pharmaceutical compositions comprising irbesartan alone or in combination with hydrochlorothiazide, which has a high content of the active, maintains a small sized dosage form and still exhibits a rapid onset of action.

Disclosure

[8] Summary of the Invention

- [9] In one general aspect there is provided a pharmaceutical composition that includes more than about 70% by weight of irbesartan or salt thereof, alone or in combination with about 2% to about 20% by weight of hydrochlorothiazide, wherein the irbesartan and the hydrochlorothiazide comprise granules with a bulk density of between about 0.35 g/ml to about 0.65 g/ml.
- [10] Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the pharmaceutical composition may further include one or more pharmaceutically acceptable excipients. Suitable pharmaceutically acceptable excipients may include one or more of diluents, binders, disintegrants, anti-adherents and lubricants.
- [11] Suitable diluents may include one or more of dibasic calcium phosphate, sugars, cellulose derivatives and mixtures thereof. For example, the diluents may be lactose hydrous, lactose anhydrous and microcrystalline cellulose. The diluents may be present at a concentration from about 1% to about 15% by weight of the tablet.
- [12] Suitable binders may include one or more of alginic acid, sodium alginate, hydroxypropyl methylcellulose, hydroxy propyl cellulose, hydroxy ethyl cellulose, methylcellulose, ethyl cellulose, gelatin, starch or starch derivatives and mixtures thereof. The binders may be present at a concentration of from about 1% to about 10% by weight of the tablet.
- [13] Suitable disintegrants may include one or more of cross-linked carboxymethyl cellulose sodium, sodium starch glycolate, pregelatinized starch, cross-linked polyvinyl pyrrolidone, low-substituted hydroxy propyl cellulose and mixtures thereof. The disintegrants may be present at a concentration of from about 1% to about 6% by

weight of the tablet.

- [14] Suitable lubricants may include one or more of calcium stearate, magnesium stearate, glyceryl monostearate, glyceryl palmitostearate, zinc stearate, sodium stearyl fumarate and stearic acid; sodium lauryl sulphate, polyethylene glycol, hydrogenated vegetable oil, talc, sodium benzoate and mixtures thereof. The lubricants may be present at a concentration of from about 0.2% to about 2% by weight of the tablet.
- [15] Suitable antiadherents may include one or more of silicon dioxide, magnesium trisilicate, talc and mixtures thereof. The antiadherents may be present at a concentration of from about 0.2% to about 2% by weight of the tablet.
- [16] The pharmaceutical composition may further include from about 1% to about 10% by weight of diluent; from about 1% to about 10% by weight of binder; from about 1% to about 6% by weight of disintegrant; from about 0.2% to about 2% by weight of lubricant; and from about 0.2% to about 2% by weight of anti-adherent.
- [17] The pharmaceutical composition may further include 8% by weight of micro-crystalline cellulose, 2% by weight of hydroxypropyl methylcellulose, 2% by weight of cross-linked carboxymethyl cellulose sodium, 1% by weight of colloidal silicon dioxide and 0.85% by weight of calcium stearate.
- [18] In another general aspect there is provided granules that include more than about 70% by weight of irbesartan or salt thereof, alone or in combination with about 2% to about 20% by weight of hydrochlorothiazide, wherein the granules have a bulk density of between about 0.35 g/ml to about 0.65 g/ml.
- [19] In another general aspect there is provided a process for the preparation of a pharmaceutical composition. The process includes blending irbesartan with one or more pharmaceutically acceptable excipients and optionally hydrochlorothiazide; granulating to obtain a wet mass; screening the wet mass to form granules; drying and sizing the granules, wherein the granules have a bulk density of between about 0.35 g/ml to about 0.65 g/ml; and compressing the granules into tablets.
- [20] Embodiments of the process may include one or more of the following features. For example, the granulation may be carried out by wet or dry granulation.
- [21] In another general aspect there is provided a process for the preparation of a pharmaceutical composition. The process includes preparing an intragranular composition by:
- [22] a) mixing irbesartan, binders, portions of diluents, antiadherent, and optionally hydrochlorothiazide, to form a powder blend;
- [23] b) granulating the powder blend with water to form a wet mass;
- [24] c) screening the wet mass to form granules; and
- [25] d) drying the granules and sizing the dried granules, wherein the granules have a bulk density of between about 0.35 g/ml to about 0.65 g/ml.

- [26] Next, the process includes preparing an extra granular composition by:
- [27] a) mixing the disintegrant and the remaining portion of the diluents and antiadherent;
- [28] b) blending the granules of the intragranular composition with the blend of extra granular composition to form the granule blend;
- [29] c) lubricating the granule blend; and
- [30] d) compressing the lubricated granule blend to form tablets.
- [31] Embodiments of the process may include one or more of the following features. For example, the granulation may be carried out by wet or dry granulation.
- [32] In another general aspect there is provided a method for the treatment of hypertension in a patient in need thereof. The method comprises administering a pharmaceutical composition comprising more than 70% by weight of irbesartan or salt thereof, alone or in combination with about 2% to about 20% by weight of hydrochlorothiazide, wherein the irbesartan and hydrochlorothiazide comprise granules with a bulk density of between about 0.35 g/ml to about 0.65 g/ml.
- [33] Detailed Description of the Invention
- [34] The inventors have now discovered that tablet dosage forms comprising irbesartan alone, or in combination with hydrochlorothiazide, may be formulated, wherein the tablet is small even though the amount of active ingredient is high.
- [35] The tablet may include more than 70% by weight of irbesartan or salt thereof alone or in combination with about 2% to about 20% by weight of hydrochlorothiazide, wherein the bulk density of the granules is between 0.35 g/ml to 0.65 g/ml.
- [36] Also provided are granules prepared according to the present invention which may be formulated into a suitable pharmaceutical composition. The granules have good flowability, reduced sticking tendency and good compressibility. Further, they result in a dosage form that is smaller in size than was previously possible for a given unit dose.
- [37] The tablets prepared may include (per tablet) from about 25 mg to about 300 mg of irbesartan, more particularly, from about 75 mg to 300 mg of irbesartan and, optionally, from about 1 mg to about 25 mg of hydrochlorothiazide, particularly from about 6.25 mg to about 12.5 mg of hydrochlorothiazide. The total weight of the tablets prepared may be from about 50 mg to about 430 mg.
- [38] For example, the tablet may be a unit dose of about 150 mg of irbesartan and a unit dose of 12.5 mg hydrochlorothiazide, wherein the total weight of the tablet does not exceed 215 mg.
- [39] The tablet may also be a unit dose of about 300 mg of irbesartan and optionally, a unit dose of 12.5 mg hydrochlorothiazide, wherein the total weight of the tablet does not exceed 430 mg.
- [40] The tablets possess desirable physical properties (hardness, friability and disin-

tegration) and are prepared in a size easy to swallow while still containing the entire required dose for single administration, thereby encouraging patient compliance. These improved tableting and flow properties are not only observed in a lab-scale batch but also in a scale-up batch, thus indicating reproducibility and consistency.

- [41] The high active ingredient content in the composition is achieved by incorporating lesser amounts of excipients. The tablets may further include one or more pharmaceutically excipients, which impart the desired cohesiveness, lubrication and free flowing properties to the active ingredients. These excipients may include one or more of binders, lubricants, diluents, anti-adherents and disintegrants.
- [42] Suitable diluents may include one or more of dibasic calcium phosphate, sugars, such as, lactose hydrous or lactose anhydrous; and cellulose or cellulose derivatives, such as, microcrystalline cellulose. For example, the diluent may be microcrystalline cellulose. The diluents may be present at a concentration from about 1% to about 15% by weight of the tablet.
- [43] Suitable binders may include alginic acid, sodium alginate; cellulose derivatives, such as hydroxypropyl methylcellulose, hydroxy propyl cellulose, hydroxy ethyl cellulose, methylcellulose and ethyl cellulose; gelatin and starch or starch derivatives. For example, the binder may be hydroxypropyl methylcellulose. The binders may be present at a concentration from about 1% to about 10% by weight of the tablets.
- [44] Suitable disintegrants may include one or more of carboxymethyl cellulose sodium (cross-linked), sodium starch glycolate, pregelatinized starch, cross-linked polyvinyl pyrrolidone and low-substituted hydroxy propyl cellulose. For example, the disintegrant may be cross-linked carboxy methylcellulose sodium. The disintegrants may be present at a concentration from about 1% to about 6% by weight of the tablets.
- [45] Suitable lubricants may include one or more of fatty acids or fatty acid derivatives, such as, calcium stearate, magnesium stearate, glyceryl monostearate, glyceryl palmitostearate, zinc stearate, sodium stearyl fumarate, stearic acid, sodium lauryl sulphate, polyethylene glycol, hydrogenated vegetable oil, talc and sodium benzoate. For example, the lubricant may be calcium stearate. The lubricants may be present a concentration from about 0.2% to about 2% by weight of the tablets.
- [46] Suitable antiadherents may include one or more of silicon-containing compounds, such as, colloidal silicon dioxide, magnesium trisilicate and talc. For example, the antiadherent may be colloidal silicon dioxide. The antiadherents may be present at a concentration from about 0.2% to 2% by weight of the tablets.
- [47] Also provided is a process of preparing the pharmaceutical composition of the present invention. The process includes:
- [48] mixing or blending the active(s) and the one or more pharmaceutically acceptable excipients;

- [49] granulating the blend;
- [50] sizing and lubricating the granules; and
- [51] compressing the granules into a suitable dosage form.
- [52] The tablets may be prepared using either wet granulation or dry granulation processes.
- [53] Also provided is a process for preparing tablets comprising more than 70% by weight of irbesartan or salt thereof, alone or in combination with 2 to 20% by weight of hydrochlorothiazide, wherein the bulk density of the granules is between 0.35 g/ml to 0.65 g/ml.
- [54] The process includes:
- [55] blending irbesartan, and one or more pharmaceutically acceptable excipients, and optionally hydrochlorothiazide to form a blend;
- [56] granulating the blend to obtain a wet mass;
- [57] screening, drying and sizing the granules, wherein the bulk density of the granules is between 0.35 g/ml to 0.65 g/ml; and
- [58] compressing the granules into tablets.
- [59] According to another embodiment, the process for preparing tablets containing irbesartan alone or in combination with hydrochlorothiazide, includes:
- [60] preparing an intragranular composition by:
- [61] mixing irbesartan, binder, portions of diluents, antiadherent and optionally hydrochlorothiazide to form a powder blend;
- [62] granulating the powder blend with water to form a wet mass;
- [63] screening the wet mass to form granules;
- [64] drying the granules and sizing the dried granules;
- [65] preparing an extra granular composition by:
- [66] mixing disintegrant and the remaining portion of the diluents and anti adherent;
- [67] blending the granules of the intragranular composition with the blend of extra granular composition to form the granule blend, wherein the bulk density of the granule blend is between 0.35 g/ml to 0.65 g/ml;
- [68] lubricating the granule blend; and
- [69] compressing the lubricated granule blend to form tablets.
- [70] The wet granulation may also be performed with an aqueous solution of the binder.
- [71] In another embodiment, the tablets may be prepared using a dry granulation process. The process includes:
- [72] blending irbesartan with one or more pharmaceutically acceptable excipients, and optionally, hydrochlorothiazide to form a blend;
- [73] compacting or slugging the blend;
- [74] milling the compacts or slugs, screening, and sizing the granules, wherein the bulk

- density of the granules is between 0.35 g/ml to 0.65 g/ml; and
- [75] compressing the granules into tablets.
- [76] The tablets prepared according to the present invention exhibit a dissolution profile wherein at least 60% of the hydrochlorothiazide is released in 30 minutes and at least 90% of the irbesartan releases in 30 minutes in a 900 ml of 0.1 N hydrochloric acid at 37°C, with paddle speed of 50 rpm using USP Apparatus II.
- [77] The powder blend of actives and excipients is formed using a mixer, such as a planetary or high shear granulator. Conventional powder mixers, such as, double cone blenders, V-shell blenders, ribbon and paddle mixers may also be used.
- [78] Dry granulation may be carried out using roller compactors or conventional tableting machines to prepare compacts or slugs.
- [79] Wet granulation is carried out using a granulator selected from amongst shear granulators, such as planetary mixers and oscillating granulators; high-speed mixer/granulators such as diosna and collette-gral mixer; and fluidized bed granulators.
- [80] The granules may be dried using conventional drying ovens, tray dryers or fluidized bed granulators. The dried granules may be milled and sized in a hammer mill or by screening.
- [81] The bulk density of the granules is determined by measuring the volume of a known mass of a test sample that has passed through a screen into a graduated cylinder (Method I described in US Pharmacopoeia). A quantity of granules 'M' having an untapped apparent volume of 150 to 250 ml is selected. According to the test, these granules are passed through a screen into a dry graduated cylinder without compacting. The material is carefully leveled without tamping and the unsettled apparent volume 'V' to the nearest graduated unit is noted. The bulk density (g/ml) is calculated by the formula:
- [82] $(M) / (V)$
- [83] The tablets may also contain one or more additional ingredients including flavors, sweeteners, colorants and preservatives. Tablets may additionally be provided with non-functional coatings. The coatings may include film-forming polymers, such as cellulose ethers, acrylic polymer or a mixture of polymers. Suitable cellulose ethers may include hydroxypropyl cellulose and hydroxypropyl methylcellulose.
- [84] Also provided is a method for the treatment of hypertension in a patient in need thereof. The method includes administering to a patient in need of a pharmaceutical composition comprising more than 70% by weight of irbesartan or salt thereof, alone or in combination with 2 to 20% by weight of hydrochlorothiazide, wherein the bulk density of the granules is between 0.35 g/ml to 0.65 g/ml.
- [85] The following examples are intended to illustrate the invention and are not to be construed as limiting the scope of the invention in any way.

[86] EXAMPLE 1

[87]

	Ingredients	Percent w/w
Intragranular	Irbesartan	83.33
	Hydrochlorothiazide	3.49
	Hydroxypropyl methylcellulose	1.68
	Colloidal silicon dioxide	0.43
	Microcrystalline cellulose	2.78
	Purified Water	Qs
Extragranular	Microcrystalline cellulose	5.34
	Cross-linked carboxymethyl cellulose sodium	1.68
	Colloidal silicon dioxide	0.43
	Calcium stearate	0.84

[88] Procedure:

[89]

1. Irbesartan, hydrochlorothiazide, hydroxypropyl methylcellulose, a portion of microcrystalline cellulose and colloidal silicon dioxide were blended and the powder was screened.
2. The powder blend was granulated with purified water to form a wet mass.
3. The wet mass was screened to form granules.
4. The granules were dried and the dried granules were screened.
5. The remaining portion of microcrystalline cellulose and colloidal silicon dioxide were blended with cross-linked carboxymethyl cellulose.
6. The powder blend of step 5 was mixed with the granules of step 4 and then lubricated with calcium stearate.
7. The mixture of step 6 was compressed into tablets.

[90] Tables 1 and 2 provide the in-vitro dissolution profiles of irbesartan and hydrochlorothiazide, respectively, prepared by the composition and process of Example 1 in 0.1N Hydrochloric acid (900 ml) at 37±0.5°C, using USP 2 apparatus at 50 rpm.

[91] Table 1: Dissolution profile of irbesartan from tablets prepared as per Example 1 in 0.1N Hydrochloric acid (900 ml), USP 2 at 50 rpm.

[92]

Time (minutes)	Percent release (%) of irbesartan from tablets of Example 1
----------------	---

5	74
10	88
20	93
30	95
45	95

[93] Table 2: Dissolution profile of hydrochlorothiazide from tablets prepared as per Example 1 in 0.1N Hydrochloric acid (900 ml), USP 2 at 50 rpm.

[94]

Time (minutes)	Percent release of hydrochlorothiazide from tablets of Example 1 (%)
5	78
10	90
20	94
30	96
45	97

[95] Table 3 provides the bulk density of the granules prepared for a lab-scale batch and scale-up batch (1,00,000 tablets).

[96] Table 3: Bulk Density of Example 1

[97]

	Lab-scale batch	Scale-up batch
Bulk Density (g/ml)	0.44	0.45

[98] Table 4 provides the physical properties of the tablets prepared for a lab-scale batch and a scale-up batch.

[99] Table 4: Physical Properties of Tablets Prepared According to Example 1

[100]

	Hardness (kilopascals)	Friability (%)	Disintegration time (minutes)
Lab-scale batch	6-12	0.48	1-2
Scale-up batch	8-11	0.21	1-2

[101] EXAMPLE 2

[102]

	Ingredients	Percent w/w
--	-------------	-------------

Intragranular	Irbesartan	80.64
	Hydrochlorothiazide	6.72
	Hydroxypropyl methylcellulose	1.61
	Colloidal silicon dioxide	0.41
	Microcrystalline cellulose	2.7
	Purified Water	Qs
Extragranular	Microcrystalline cellulose	4.92
	Cross-linked carboxymethyl cellulose sodium	1.61
	Colloidal silicon dioxide	0.41
	Iron oxide	0.17
	Calcium stearate	0.81

[103] Procedure: Similar to Example 1.

[104] EXAMPLE 3

[105]

	Ingredients	Percent w/w
Intragranular	Irbesartan	81.0
	Hydrochlorothiazide	3.49
	Hydroxypropyl cellulose	1.68
	Colloidal silicon dioxide	0.43
	Microcrystalline cellulose	3.78
	Purified Water	Qs
Extragranular	Microcrystalline cellulose	6.67
	Cross-linked carboxymethyl cellulose sodium	1.68
	Colloidal silicon dioxide	0.43
	Calcium stearate	0.84

[106] Procedure:

[107]

1. Blend irbesartan, hydrochlorothiazide, hydroxy propylcellulose, a portion of microcrystalline cellulose and colloidal silicon dioxide and screen the powder.

2. Granulate the powder blend with purified water to form a wet mass.
3. Screen the wet mass to form granules.
4. Dry and screen the granules.
5. Blend the remaining portion of microcrystalline cellulose and colloidal silicon dioxide with cross-linked carboxymethyl cellulose.
6. Mix the powder blend of step 5 with the granules of step 4 and lubricate with calcium stearate.
7. Compress the mixture of step 6 into tablets.

[108] EXAMPLE 4

[109]

	Ingredients	Percent w/w
Intragranular	Irbesartan	78.49
	Methylcellulose	3.68
	Colloidal silicon dioxide	0.53
	Microcrystalline cellulose	4.78
	Purified Water	Qs
Extragranular	Microcrystalline cellulose	7.34
	Cross-linked carboxymethyl cellulose sodium	3.68
	Colloidal silicon dioxide	0.53
	Calcium stearate	0.84

[110] Procedure: Similar to Example 3.

[111] While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

Claims

- [1] A pharmaceutical composition comprising more than about 70% by weight of irbesartan or salt thereof, alone or in combination with about 2% to about 20% by weight of hydrochlorothiazide, wherein the irbesartan and the hydrochlorothiazide comprise granules with a bulk density of between about 0.35 g/ml to about 0.65 g/ml.
- [2] The pharmaceutical composition of claim 1, further comprising one or more pharmaceutically acceptable excipients.
- [3] The pharmaceutical composition of claim 2, wherein the one or more pharmaceutically acceptable excipients comprise diluents, binders, disintegrants, anti-adherents and lubricants.
- [4] The pharmaceutical composition of claim 3, wherein the diluents comprise dibasic calcium phosphate, sugars, cellulose derivatives and mixtures thereof.
- [5] The pharmaceutical composition of claim 4, wherein the cellulose derivatives comprise lactose hydrous, lactose anhydrous and microcrystalline cellulose.
- [6] The pharmaceutical composition of claim 3, wherein the diluents comprise from about 1% to about 15% by weight of the tablet.
- [7] The pharmaceutical composition of claim 3, wherein the binders comprise alginic acid, sodium alginate, hydroxypropyl methylcellulose, hydroxy propyl cellulose, hydroxy ethyl cellulose, methylcellulose, ethyl cellulose, gelatin, starch or starch derivatives and mixtures thereof.
- [8] The pharmaceutical composition of claim 3, wherein the binders comprise from about 1% to about 10% by weight of the tablet.
- [9] The pharmaceutical composition of claim 3, wherein the disintegrants comprise cross-linked carboxymethyl cellulose sodium, sodium starch glycolate, pregelatinized starch, cross-linked polyvinyl pyrrolidone, low-substituted hydroxy propyl cellulose and mixtures thereof.
- [10] The pharmaceutical composition of claim 3, wherein the disintegrants comprise from about 1% to about 6% by weight of the tablet.
- [11] The pharmaceutical composition of claim 3, wherein the lubricants comprise calcium stearate, magnesium stearate, glyceryl monostearate, glyceryl palmitostearate, zinc stearate, sodium stearyl fumarate, stearic acid, sodium lauryl sulphate, polyethylene glycol, hydrogenated vegetable oil, talc, sodium benzoate and mixtures thereof.
- [12] The pharmaceutical composition of claim 3, wherein the lubricants comprise from about 0.2% to about 2% by weight of the tablet.
- [13] The pharmaceutical composition of claim 3, wherein the antiadherents comprise

silicon dioxide, magnesium trisilicate, talc and mixtures thereof.

[14] The pharmaceutical composition of claim 13, wherein the antiadherents comprise from about 0.2% to about 2% by weight of the tablet.

[15] The pharmaceutical composition of claim 1, further comprising:

- i) from about 1% to about 10% by weight of diluent;
- ii) from about 1% to about 10% by weight of binder;
- iii) from about 1% to about 6% by weight of disintegrant;
- iv) from about 0.2% to about 2% by weight of lubricant; and
- v) from about 0.2% to about 2% by weight of anti-adherent.

[16] The pharmaceutical composition of claim 1, further comprising 8% by weight of microcrystalline cellulose, 2% by weight of hydroxypropyl methylcellulose, 2% by weight of cross-linked carboxymethyl cellulose sodium, 1% by weight of colloidal silicon dioxide and 0.85% by weight of calcium stearate.

[17] Granules comprising more than about 70% by weight of irbesartan or salt thereof, alone or in combination with about 2% to about 20% by weight of hydrochlorothiazide, wherein the granules have a bulk density of between about 0.35 g/ml to about 0.65 g/ml.

[18] A process for the preparation of a pharmaceutical composition, the process comprising the steps of:

- i) blending irbesartan with one or more pharmaceutically acceptable excipients and optionally hydrochlorothiazide;
- ii) granulating to obtain a wet mass;
- iii) screening the wet mass to form granules;
- iv) drying and sizing the granules, wherein the dried and sized granules have a bulk density of between about 0.35 g/ml to about 0.65 g/ml; and
- v) compressing the granules into tablets.

[19] The process of claim 18, wherein the granulation may be carried out by wet or dry granulation.

[20] A process for the preparation of a pharmaceutical composition, the process comprising the steps of:

- 1. preparing an intragranular composition by:
 - a) mixing irbesartan, binder, diluent, antiadherent, and optionally hydrochlorothiazide, to form a powder blend;
 - b) granulating the powder blend with water to form a wet mass;
 - c) screening the wet mass to form granules; and
 - d) drying the granules and sizing the dried granules; wherein the granules have a bulk density of between about 0.35 g/ml to about 0.65 g/ml

2. preparing an extra granular composition by mixing disintegrant, diluent and anti adherent;
3. blending the granules of the intragranular composition with extra granular composition to form a granule blend;
4. lubricating the granule blend; and
5. compressing the lubricated granule blend to form tablets.

[21] The process of claim 20, wherein the granulation may be carried out by wet or dry granulation.

[22] A method for the treatment of hypertension in a patient in need thereof, the method comprising administering a pharmaceutical composition comprising more than 70% by weight of irbesartan or salt thereof, alone or in combination with about 2% to about 20% by weight of hydrochlorothiazide, wherein the irbesartan and hydrochlorothiazide comprise granules with a bulk density of between about 0.35 g/ml to about 0.65 g/ml.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/052549

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/415 A61K31/54 A61K9/20

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 practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 275 391 A (SANOFI-SYNTHELABO) 15 January 2003 (2003-01-15) the whole document	1-22
A	EP 0 747 050 A (BRISTOL-MYERS SQUIBB COMPANY; SANOFI-SYNTHELABO) 11 December 1996 (1996-12-11) the whole document	1-22
A	US 2002/076437 A1 (KOTHARI SANJEEV ET AL) 20 June 2002 (2002-06-20) the whole document	1-22



Further documents are listed in the continuation of box C.



Patent family members are listed in 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 document 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

6 December 2005

Date of mailing of the international search report

16/12/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Toulacis, C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/052549

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 22 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB2005/052549

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1275391	A	15-01-2003	NONE
EP 0747050	A	11-12-1996	AT 248594 T 15-09-2003
		AU 702651 B2 25-02-1999	
		AU 5476396 A 19-12-1996	
		CA 2177772 A1 08-12-1996	
		CN 1144656 A 12-03-1997	
		CZ 9601634 A3 11-12-1996	
		DE 69629755 D1 09-10-2003	
		DE 69629755 T2 01-07-2004	
		DK 747050 T3 15-12-2003	
		ES 2205000 T3 01-05-2004	
		HK 1002384 A1 05-03-2004	
		HU 9601564 A2 28-09-1998	
		IL 118309 A 24-06-2003	
		JP 3162626 B2 08-05-2001	
		JP 8333253 A 17-12-1996	
		NO 962387 A 09-12-1996	
		NO 20004743 A 09-12-1996	
		NZ 286612 A 25-03-1998	
		PL 314670 A1 09-12-1996	
		PT 747050 T 31-12-2003	
		RU 2181590 C2 27-04-2002	
		RU 2210368 C1 20-08-2003	
		SG 49956 A1 15-06-1998	
		TW 442301 B 23-06-2001	
		ZA 9604337 A 28-11-1997	
US 2002076437	A1	20-06-2002	NONE