

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
23 March 2006 (23.03.2006)

PCT

(10) International Publication Number
WO 2006/030303 A1

(51) International Patent Classification:

A61K 31/155 (2006.01) A61K 9/20 (2006.01)
A61K 31/375 (2006.01) A61K 9/48 (2006.01)
A61K 31/64 (2006.01) A61P 3/10 (2006.01)

(21) International Application Number:

PCT/IB2005/002753

(22) International Filing Date:

16 September 2005 (16.09.2005)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

1769/DEL/2004 17 September 2004 (17.09.2004) IN

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(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, LY, 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

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: ORAL EXTEND RELEASE DOSAGE FORM COMPRISING A HIGH DOSE BIGUANIDE AND A LOW DOSE SULFONYLUREA

(57) Abstract: The present invention relates to orally administered extended release pharmaceutical compositions that include a combination of: a/ a highly water-soluble, high dose biguanide in an extend release form and b/ a water-insoluble low dose sulfonylurea in an extend release form.



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ORAL EXTENDED RELEASE DOSAGE FORM COMPRISING A HIGH DOSE BIGUANIDE AND A LOW DOSE SULFONYLUREA

Technical Field of the Invention

5 The present invention relates to orally administered extended release pharmaceutical compositions that include a combination of highly water-soluble, high dose metformin and water-insoluble, low-dose glimepiride.

Background of the Invention

Diabetes mellitus is a term generally used to refer to various pathological states
10 characterized by hyperglycemia and altered metabolism of lipids, carbohydrates and proteins. Diabetic conditions are generally classified as either insulin-dependent diabetes mellitus (IDDM, Type I diabetes) or non-insulin-dependent diabetes mellitus (NIDDM, Type II diabetes).

Virtually all forms of diabetes are due to a decrease in the circulating concentration
15 of insulin (insulin deficiency) and/or a decrease in the response of peripheral tissues to insulin (insulin resistance). These abnormalities lead to alterations in the metabolism of carbohydrates, lipids, ketones and amino acids, and a hyperglycemic condition. IDDM appears to have an autoimmune etiology that results in destruction of Beta-islet cells in the pancreas and leads to an inability to produce insulin. The etiology of NIDDM, the most
20 prevalent form of diabetes, is more complex and possibly heterogeneous.

NIDDM, also known as diabetes mellitus of type II, is a progressive metabolic disorder with diverse pathologic manifestations and is often associated with carbohydrate and lipid metabolic disorders. The long-term effects of diabetes result from its vascular complications, such as the microvascular complications of retinopathy, neuropathy and
25 nephropathy, and the macrovascular complications of cardiovascular, cerebrovascular and peripheral vascular diseases. Initially, diet and exercise is the mainstay of treatment of type II diabetes. However, these are followed by administration of oral hypoglycemic agents. Current drugs used for managing type II diabetes and its precursor syndromes, such as insulin resistance, include classes of compounds such as, for example, biguanides
30 and sulfonylureas, among others.

Biguanides, represented by metformin, phenformin and buformin, help in the control of blood glucose by decreasing hepatic glucose production and reducing intestinal absorption of glucose. Metformin has been widely prescribed for lowering blood glucose in patients with NIDDM, is marketed as Glucophage® tablets containing 500 mg, 850 mg, or 1000 mg of metformin hydrochloride, and has a maximum recommended dose of 2550 mg per day. However, being a short acting drug, metformin requires twice-daily or three-times-a-day dosing (500-850 mg tab 2-3x/day or 1000 mg bid with meals).

Sulfonylureas, represented principally by glipizide, glimepiride, glyburide, glibonuride, glisoxepide, gliclazide acetohexamide, chlorpropamide, tolazamide, and tolbutamide, among others, help in controlling or managing NIDDM by stimulating the release of insulin from the pancreas.

Biguanides, especially metformin, improve glucose tolerance but cannot stimulate insulin secretion. Sulfonylureas lower blood glucose levels acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. A combination therapy of a biguanide and a sulfonylurea has a synergistic effect on glucose control, since both agents act by different but complementary mechanisms.

These agents are often given in combination with drugs that increase the output of insulin from the pancreas, such as the sulfonylureas. This combination sometimes results in greater efficacy, the ability to use lower doses of the drugs, and a reduced adverse side effect profile. Adverse events associated with the administration of biguanides include anorexia, nausea, vomiting and diarrhea. The adverse events may be partially avoided by either reducing the initial and/or maintenance dose using an extended-release dosage form. Another advantage of an extended-release dosage form is a reduction in the frequency of administration. Findings suggest that extended-release dosage forms of a biguanide may improve the quality of therapy in patients with NIDDM.

Studies have shown that a combination of insulin secretion enhancers and insulin sensitivity enhancers has a remarkable effect on glycemic control. The different mechanisms of action in targeting hyperglycemia are complimentary and capable of providing a remedy for both the deficiency in insulin secretion and insulin sensitivity conditions. The combination therapy therefore plays an important therapeutic role

because it provides an effective metabolic control in NIDDM patients in whom therapy with either sulfonylureas or biguanides alone becomes ineffective with time.

The use of combinations of metformin (a biguanide) and glyburide (a sulfonylurea) has been demonstrated to be synergistic in clinical trials when compared with the use of the individual agents separately (see Physician's Desk Reference 2000, page 832). The monograph also discloses the use of combinations of metformin and sulfonylureas for patients not controlled on metformin alone. Several references pertain to pharmaceutical compositions having combinations of biguanides and sulfonylureas providing for controlled or immediate release of both of the drugs.

Biguanide-sulphonylurea combinations such as metformin-glyburide and metformin-glipizide are commercially available as Glucovance® and Metaglip™ as single dosage forms from Bristol Myers Squibb.

Glimepiride is a second-generation sulfonylurea with a long half-life, which ranges from five to nine hours. Upon administration as a conventional tablet the absolute bioavailability of glimepiride is 100% with a T_{max} being reached between two and four hours. Currently, glimepiride is administered as once-a-day conventional tablet dosage form.

Clinical studies have revealed that adequate metabolic control with glimepiride once-a-day therapy was not achieved as evident from high fasting plasma glucose (FPG) levels. The dose titration on the basis of FPG levels demonstrated that a twice-a-day regimen was needed to achieve the required metabolic control in NIDDM patients.

Further, since glimepiride belongs to Class II as per the Biopharmaceutics Classification System, i.e., a drug with high permeability and low solubility, it is a suitable candidate for development into an extended release dosage form.

Extended release dosage forms not only increase patient compliance due to reduction in frequency of dosing, but they also reduce the severity and frequency of side-effects as they maintain substantially constant blood levels and avoid fluctuations associated with the conventional immediate release formulations. Adverse events associated with glimepiride use include hypoglycemia, weight gain, etc. An inverse relationship has been reported between the Fasting Plasma Glucose levels and glimepiride dose. The episodes of hypoglycemia have often been linked to the high plasma drug

concentration of glimepiride due to rapid absorption of glimepiride with conventional immediate release formulations. These adverse effects may be partially avoided by administering glimepiride in an extended release dosage form.

5 Extended release tablets that employ either a biguanide alone or a sulfonylurea drug alone have been described in the prior art. For example, WO 96/08243 discloses a controlled release dosage form that contains only metformin hydrochloride as the active ingredient, and employs a hydrogel to push the active ingredient from the dosage form.

Similarly, U.S. Patent Nos. 5,545,413; 5,591,454; and 5,091,190 disclose controlled release osmotic dosage forms that contain only the drug glipizide, and employ a
10 hydrogel to push the active ingredient from the dosage form.

U.S. Patent Nos. 6,099,862 and 6,284,275 describe a combination composition for the simultaneous controlled release of a biguanide (metformin) and a sulfonylurea (glipizide). The composition comprises a core containing the two active agents along with other excipients and a semipermeable controlled release coating from which the release of
15 the active agents is controlled by the presence of at least one passageway in the coat.

Although combinations of two antidiabetic agents are well known in the art and are convenient to formulate, a combination of extended release pharmaceutical compositions of a water-soluble active, i.e., a biguanide, and a water-insoluble or sparingly soluble active, i.e., a sulfonylurea, is difficult to achieve using a simple and cost-effective process.
20 The prior art teaches osmotic dosage forms which are quite complicated to design.

Further, formulating a metformin/glimepiride extended release combination in a single tablet poses many challenges. First, the dose for each agent is very different. Metformin is available commercially as a tablet in the dose range of 500-1000 mg. Glimepiride is available as 1 mg, 2 mg and 4 mg tablets. Given the disparity in the doses
25 of the two actives, content uniformity of glimepiride poses significant problems.

Therefore, it would be prudent to design an extended release formulation of glimepiride to be administered either alone or in combination with an extended release formulation of a biguanide. Additional advantages of an extended release formulation of glimepiride include achieving a lower peak plasma concentration, lower fluctuation index
30 and invariably a better metabolic control as compared to the conventional therapy.

Summary of the Invention

In one general aspect there is provided a pharmaceutical composition of antidiabetic agents for oral administration. The composition includes (a) a highly water-soluble, high dose biguanide in an extended release form; and (b) a water-insoluble, low dose sulfonylurea in an extended release form.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the biguanide may be one or more of metformin, phenformin and buformin. The sulfonylurea may be one or more of glipizide, glimepiride, glibornuride, glyburide, glisozepide, gliclazide, acetohexamide, chlorpropamide, tolazamide and tolbutamide.

The composition may be a reservoir type formulation, a matrix type formulation, or combinations of both. The extended release formulations may be prepared as a reservoir type, matrix type or a combination thereof. Reservoir type formulations utilize polymeric coating over the core of the drug and matrix-type formulations are those in which the drug is distributed uniformly in an inert polymeric matrix. A combination of the reservoir and matrix type includes extended or sustained release coatings on extended release matrices. The matrix type dosage form may be a uniform mixture of biguanide or sulfonylurea and one or more rate controlling polymers.

The extended release pharmaceutical compositions may be present in the form of multiparticulates, such as particles, beads or granules. The coated or uncoated multiparticulates of biguanide and sulfonylurea may be filled into capsules.

Alternatively, separate mixture of biguanide with one or more of rate-controlling polymers and mixture of sulfonylurea with one or more rate-controlling polymers may be compressed into bilayered tablets.

The composition may further include one or more rate-controlling polymers and pharmaceutically acceptable excipients. The rate-controlling polymers may include hydrophilic polymers, hydrophobic polymers, or a combination thereof. The hydrophilic rate-controlling polymer may be one or more of cellulose derivatives, polyvinylpyrrolidone, polysaccharides, polyalkylene glycols, starch and derivatives.

The pharmaceutically acceptable excipients may be one or more of fillers, binders, lubricants, glidants, colorants and flavoring agents. The filler may be one or more of corn starch, lactose, white sugar, sucrose, sugar compressible, sugar confectioners, glucose, sorbitol, calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrans, dextrose, fructose, kaolin, lactitol, mannitol, sorbitol, starch, starch pregelatinized and sucrose. The binder may be one or more of methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, pullutan, pregelatinized starch, agar, tragacanth, sodium alginate and propylene glycol. The lubricant and glidant may be one or more of colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax and white beeswax.

The pharmaceutical composition may be a tablet or a capsule.

The metformin in the composition may have a T_{max} , C_{max} , AUC_{0-last} , and $AUC_{0-\infty}$ when administered under fed conditions that are comparable to the respective values of the metformin in Glucophage XR when administered under fed conditions. The glimepiride in the composition may have a T_{max} , C_{max} , AUC_{0-last} , and $AUC_{0-\infty}$ when administered under fed conditions that are comparable to the respective values of the metformin in Amaryl when administered under fed conditions.

In another general aspect there is provided a process for preparing an extended release pharmaceutical composition of antidiabetic agents for oral administration in the form of a combination of highly water-soluble, high dose biguanide and water-insoluble, low dose sulfonylurea. The process includes the steps of (a) blending one or more biguanides with one or more rate-controlling polymers and pharmaceutically acceptable excipients, (b) blending one or more sulfonylurea with one or more rate-controlling polymers and pharmaceutically acceptable excipients, and (c) formulating the blends of (a) and (b) into a pharmaceutical composition.

Embodiments may include one or more of the following features or those described above. For example, the blend may be formulated into a tablet or capsule. The tablet may be a bilayered tablet.

In another general aspect there is provided a method of treating non-insulin-dependent diabetes mellitus by administering to a person in need thereof an extended release pharmaceutical composition that includes a combination of a highly water-soluble, high dose biguanide and a water-insoluble, low dose sulfonylurea. The composition provides extended-release of both metformin and glimepiride.

Embodiments may include one or more of the following features or those described above. For example, the metformin in the composition may have a T_{max} , C_{max} , AUC_{0-last} , and $AUC_{0-\infty}$ when administered under fed conditions that are comparable to the respective values of the metformin in Glucophage XR when administered under fed conditions. The glimepiride in the composition may have a T_{max} , C_{max} , AUC_{0-last} , and $AUC_{0-\infty}$ when administered under fed conditions that are comparable to the respective values of the metformin in Amaryl when administered under fed conditions.

The dosage form may further include one or more pharmaceutically acceptable excipients and may take shape of tablets or capsules.

In the embodiment of the above process, the blend may be granulated to form multiparticulates, such as particles, beads or granules. The multiparticulates of biguanide and sulfonylurea may be filled into capsules or compressed to form bilayered or multilayered tablets.

It is yet another aspect to provide a method of treating non-insulin-dependent diabetes mellitus (NIDDM, Type II diabetes) in a patient in need thereof. The method includes administering an extended release pharmaceutical compositions comprising of combination of highly water-soluble, high dose biguanide and water-insoluble, low dose sulfonylurea, wherein the compositions provides extended-release of both biguanide and sulfonylurea.

The extended release pharmaceutical compositions may further include one or more of glitazone, insulin, alpha-glucosidase inhibitors, meglitinides, fibrates, statins, squalene synthesis inhibitors and angiotensin-converting enzyme inhibitors.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and claims.

Detailed Description of the Invention

The present invention relates to orally administered extended release pharmaceutical compositions that include a combination of metformin and glimepiride.

5 Glimepiride particle size may be equal to or less than about 10 microns for better solubility. Size reduction or micronization may be carried out in any of the conventionally known mills, such as ball mill, colloid mill, grinding mill, air jet mill, roller mill, impact mill, etc.

10 The extended release pharmaceutical compositions of metformin as well as glimepiride may be combined using several different embodiments. The metformin and glimepiride may be present in a single unit dosage form, such as a monolithic matrix dosage forms.

The term matrix, as used herein, refers to a uniform mixture of a metformin or glimepiride, rate-controlling polymers, and one or more pharmaceutically acceptable excipients.

15 The extended release pharmaceutical compositions may be present in a tablet form in which the two actives are formulated together as a bilayered or multilayered tablet. The term "bilayered or multilayered" may encompass dosage forms where there are two separate drug layers, one on top of the other with only one surface in mutual contact or with an inert layer in between. These may also be prepared by compression granulation of one drug on a previously compressed granulation of another drug, or alternatively by feeding previously compressed tablets of one drug into a machine and compressing granulation layer of another drug on the preformed tablets.

20 The extended release pharmaceutical compositions may be multiple-compression tablets comprising an inner core of glimepiride and an outer coat of metformin, and may be prepared such that one surface of the inner core is exposed. These types of tablets are also referred to as inlay or bull's-eye tablets and these are similar to compression-coated tablets except that one surface of the coating is eliminated.

Various rate-controlling polymeric materials can be used in the matrices to achieve the type of pattern of release. The rate-controlling polymers may be hydrophilic,

hydrophobic or combinations thereof. These rate-controlling polymers may constitute from about 5% to about 60% by weight of the dosage form.

Hydrophilic rate-controlling polymers may include one or more cellulose derivatives such as hydroxypropylcellulose, hydroxypropylmethylcellulose,
5 hydroxyethylcellulose, hydroxymethylcellulose, carboxymethylcellulose, methylcellulose, sodium carboxy methylcellulose or combinations thereof; polyvinylpyrrolidone, polysaccharides, polyalkylene glycols, starch and derivatives; or mixtures thereof.

Hydrophobic polymers may be selected from one or more of ethyl cellulose, cellulose acetate, cellulose acetate butyrate, hydroxypropyl methylcellulose phthalate, poly
10 (alkyl) methacrylate, and copolymers of acrylic or methacrylic acid esters, waxes, shellac and hydrogenated vegetable oils.

In addition to the active and rate-controlling polymers, the matrix may further include other pharmaceutically acceptable excipients that act in one or more capacities as fillers, binders, lubricants, glidants, colorants or flavoring agents.

15 Suitable examples of fillers include, but are not limited to, corn starch, lactose, white sugar, sucrose, sugar compressible, sugar confectioners, glucose, sorbitol, calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrans, dextrose, fructose, kaolin, lactitol, mannitol, sorbitol, starch, starch
20 pregelatinized, sucrose, and mixtures thereof.

Examples of binders include, but are not limited to, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, pullutan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and mixtures thereof.

25 Examples of lubricants and glidants include, but are not limited to, colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax, white beeswax, and mixtures thereof.

The coloring agents of the present invention may be selected from any FDA
30 approved color for oral use.

The pharmaceutical composition may be formulated into various pharmaceutical preparations for oral administration, e.g., in the form of a tablet or capsule in accordance with any of the conventional procedures known in the field of art, for example, milling, sieving, slugging, kneading, granulating, tableting, coating, etc. These steps may be carried out in the conventional manner.

The tablets prepared by the present invention may be a bilayered or multilayered tablet with one or more layers comprising film forming agents and/or pharmaceutically acceptable excipients.

The coating layers over the tablet may be applied as solution or dispersion of coating ingredients using any conventional technique known in the art, such as spray coating in a conventional coating pan or fluidized bed processor or dip coating.

The pharmaceutical compositions according to the present invention containing extended release layers of metformin and glimepiride may be used as a combination therapy to provide an effective metabolic control in NIDDM patients in whom single therapy becomes ineffective with time.

In one of the embodiments, there is a process for preparing an extended release pharmaceutical composition of antidiabetic agents for oral administration in the form of a combination of highly water-soluble, high dose biguanide and water-insoluble, low dose sulfonylurea. The process includes the steps of:

- a) blending metformin with one or more rate-controlling polymers and pharmaceutically acceptable excipients,
- b) blending glimepiride with one or more rate-controlling polymers and pharmaceutically acceptable excipients, and
- c) compressing the blends of (a) and (b), over each other to form a bilayered tablet.

In the embodiment of the above process, the blend may be granulated to form multiparticulates, such as particles, beads or granules. The multiparticulates of metformin and glimepiride may be filled into capsules or compressed to form bilayered or multilayered tablets.

The present invention is illustrated below by reference to the following example. However, one skilled in the art will appreciate that the specific methods and results

discussed are merely illustrative of the invention, and are not to be construed as limiting the invention.

Example 1:

Bilayered tablet

	INGREDIENTS	Percent w/w of the tablet (%w/w)
<u>Glimepiride layer</u>	Glimepiride	0.19
	Hydroxy propyl methyl cellulose	7.4
	Lactose	4.63
	Microcrystalline Cellulose	5.09
	Polyvinylpyrrolidone	0.9
	Magnesium Stearate	0.09
	Talc	0.09
	Colloidal silicon dioxide	0.09
	Purified water	q.s.
<u>Metformin layer</u>	Metformin hydrochloride	46.3
	Hydroxypropyl methylcellulose	32.4
	Polyvinyl pyrrolidone	1.9
	Magnesium stearate	0.46
	Talc	0.46
	Purified Water	q.s.

5

Procedure:

Glimepiride layer

- 1) Glimepiride was blended with hydroxypropyl methylcellulose, lactose, and microcrystalline cellulose and granulated with an aqueous solution of polyvinylpyrrolidone.
- 2) The wet mass was screened, dried, sized and lubricated with magnesium stearate, talc and colloidal silicon dioxide.

Metformin layer

- 1) Metformin hydrochloride was blended with hydroxypropyl methylcellulose and granulated with an aqueous solution of polyvinylpyrrolidone.
- 2) The wet mass was screened, dried, sized and lubricated with magnesium stearate and talc.

The two layers, i.e., the metformin layer and the glimepiride layer, were compressed over each other to form a bilayered tablet.

Tables 1 provides the in-vitro release profiles of glimepiride from bilayered tablets prepared by the composition of and process of Example 1 in phosphate buffer pH 7.8 (900 ml), USP 2 at 50 rpm.

Table 1: Release profile of glimepiride from bilayered tablets prepared as per Example 1 in Phosphate buffer pH 7.8 (900 ml), USP 2 at 50 rpm.

Time (hrs)	Percent release of glimepiride from tablets of Example 1 (%)
0.5	16
1.0	28
2.0	39
4.0	52
8.0	77
12.0	92
16.0	103

Pharmacokinetic studies under fed conditions:

10 A single fixed dose combination of Metformin ER 500 mg and Glimepiride ER 2 mg bilayered tablet of Example 1 was compared with simultaneously separately administered extended-release metformin hydrochloride 500mg (GLUCOPHAGE XR tablets; Bristol Myers Squibb) and Glimepiride 2mg tablets (AMARYL™ tablets; Aventis) under fed conditions.

15 Values for pharmacokinetic parameters, including T_{MAX} , C_{MAX} , AUC_{0-last} and $AUC_{0-\infty}$ were calculated using standard non-compartmental methods and are shown in Tables 2 and 3. The results as indicated by the ratios of test to reference are shown in Table 4.

20 Reference R: GLUCOPHAGE XR 500 mg (Bristol Myers Squibb) + AMARYL tablets, 2 mg (Aventis)

Test T: Metformin ER + Glimepiride ER tablets (of Example 1)

Table 2: Summary of pharmacokinetic parameters for metformin

Product	Parameters			
	T _{MAX} (hr)	C _{MAX} (ng/mL)	AUC _{0-last} (ng.hr/mL)	AUC _{0-∞} (ng.hr/mL)
Test (T)	6.99 ± 2.99	655 ± 148	8045 ± 2227	8148 ± 2224
Reference (R)	6.94 ± 2.37	657 ± 160	8298 ± 2488	8398 ± 2492

Table 2: Summary of pharmacokinetic parameters for glimepiride

Product	Parameters			
	T _{MAX} (hr)	C _{MAX} (ng/mL)	AUC _{0-last} (ng.hr/mL)	AUC _{0-∞} (ng.hr/mL)
Test (T)	6.19 ± 2.84	174 ± 76	1649 ± 2399	1935 ± 3491
Reference (R)	4.54 ± 2.24	205 ± 108	1575 ± 2152	1849 ± 3221

- 5 While several particular forms of the inventions have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions. For example, the extended release pharmaceutical compositions may further include one or more of glitazone, insulin, alpha-glucosidase inhibitors, meglitinides, fibrates, statins, squalene
- 10 synthesis inhibitors and angiotensin-converting enzyme inhibitors. Accordingly, it is not intended that the inventions be limited, except as by the appended claims.

We Claim:

- 1 1. A pharmaceutical composition of antidiabetic agents for oral administration, the
2 composition comprising
 - 3 a) a highly water-soluble, high dose biguanide in an extended release form; and
 - 4 b) a water-insoluble, low dose sulfonylurea in an extended release form.
- 1 2. The pharmaceutical composition of claim 1, wherein the biguanide comprises one
2 or more of metformin, phenformin and buformin.
- 1 3. The pharmaceutical composition of claim 1, wherein the sulfonylurea comprises
2 one or more of glipizide, glimepiride, glibornuride, glyburide, glisozepide, gliclazide,
3 acetohexamide, chlorpropamide, tolazamide and tolbutamide.
- 1 4. The pharmaceutical composition of claim 1, wherein the composition comprises a
2 reservoir type formulation, matrix type formulation, or combinations of both.
- 1 5. The pharmaceutical composition of claim 1, wherein the composition further
2 comprises one or more rate-controlling polymers and pharmaceutically acceptable
3 excipients.
- 1 6. The pharmaceutical composition of claim 5, wherein the rate-controlling polymers
2 comprise hydrophilic polymers, hydrophobic polymers, or a combination thereof.
- 1 7. The pharmaceutical composition of claim 6 wherein the hydrophilic rate-
2 controlling polymer comprises one or more of cellulose derivatives, polyvinylpyrrolidone,
3 polysaccharides, polyalkylene glycols, starch and derivatives.
- 1 8. The pharmaceutical composition of claim 5, wherein the pharmaceutically
2 acceptable excipients comprise one or more of fillers, binders, lubricants, glidants,
3 colorants and flavoring agents.
- 1 9. The pharmaceutical composition of claim 8, wherein the filler comprises one or
2 more of corn starch, lactose, white sugar, sucrose, sugar compressible, sugar
3 confectioners, glucose, sorbitol, calcium carbonate, calcium phosphate-dibasic, calcium
4 phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline
5 cellulose, cellulose powdered, dextrans, dextrins, dextrose, fructose, kaolin, lactitol,
6 mannitol, sorbitol, starch, starch pregelatinized and sucrose.

- 1 10. The pharmaceutical composition of claim 8, wherein the binder comprises one or
2 more of methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose,
3 polyvinylpyrrolidone, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, pullutan,
4 pregelatinized starch, agar, tragacanth, sodium alginate and propylene glycol.
- 1 11. The pharmaceutical composition of claim 8, wherein the lubricant and glidant
2 comprise one or more of colloidal anhydrous silica, stearic acid, magnesium stearate,
3 calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acids,
4 microcrystalline wax, yellow beeswax and white beeswax.
- 1 12. The pharmaceutical composition of claim 1, wherein the composition comprises a
2 tablet or a capsule.
- 1 13. The pharmaceutical composition of claim 2, wherein the metformin in the
2 composition has a T_{max} , C_{max} , AUC_{0-last} , and $AUC_{0-\infty}$ when administered under fed
3 conditions that are comparable to the respective values of the metformin in Glucophage
4 XR when administered under fed conditions.
- 1 14. The pharmaceutical composition of claim 3, wherein the glimepiride in the
2 composition has a T_{max} , C_{max} , AUC_{0-last} , and $AUC_{0-\infty}$ when administered under fed
3 conditions that are comparable to the respective values of the metformin in Amaryl when
4 administered under fed conditions.
- 1 15. A process for preparing an extended release pharmaceutical composition of
2 antidiabetic agents for oral administration in the form of a combination of highly water-
3 soluble, high dose biguanide and water-insoluble, low dose sulfonylurea, the process
4 comprising the steps of:
- 5 a) blending one or more biguanides with one or more rate-controlling polymers
6 and pharmaceutically acceptable excipients,
- 7 b) blending one or more sulfonylurea with one or more rate-controlling polymers
8 and pharmaceutically acceptable excipients, and
- 9 c) formulating the blends of (a) and (b) into a pharmaceutical composition.
- 1 16. The process of claim 15 wherein the blend is formulated into a tablet or capsule.
- 1 17. The process of claim 16 wherein the tablet comprises a bilayered tablet.

1 18. A method of treating non-insulin-dependent diabetes mellitus by administering to a
2 person in need thereof an extended release pharmaceutical composition comprising
3 combination of highly water-soluble, high dose biguanide and water-insoluble, low dose
4 sulfonylurea, wherein the composition provides extended-release of both metformin and
5 glimepiride.

1 19. The method of claim 18, wherein the metformin in the composition has a T_{max} ,
2 C_{max} , AUC_{0-last} , and $AUC_{0-\infty}$ when administered under fed conditions that are comparable
3 to the respective values of the metformin in Glucophage XR when administered under fed
4 conditions.

1 20. The pharmaceutical composition of claim 18, wherein the glimepiride in the
2 composition has a T_{max} , C_{max} , AUC_{0-last} , and $AUC_{0-\infty}$ when administered under fed
3 conditions that are comparable to the respective values of the metformin in Amaryl when
4 administered under fed conditions.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/002753

A. CLASSIFICATION OF SUBJECT MATTER

A61K31/155 A61K31/375 A61K31/64 A61K9/20 A61K9/48
A61P3/10

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, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 284 275 B1 (CHEN CHIH-MING ET AL) 4 September 2001 (2001-09-04) claims 1-39 page 3, line 5 - page 5, line 45 -----	1-8, 12-14, 18-20
X	US 2003/219482 A1 (CHAUDHARI SUNIL SUDHAKAR ET AL) 27 November 2003 (2003-11-27) claims 1-33 paragraph '0028! - paragraph '0054! ----- -/--	1-8, 10, 12-16, 18-20

☒ 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.
- *Z* document member of the same patent family

Date of the actual completion of the international search

12 December 2005

Date of mailing of the international search report

22/12/2005

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INTERNATIONAL SEARCH REPORT

International Application No

PC1/IB2005/002753

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ARNO-E-A. ANAND-P. BHASKAR-K. RAMACHANDRAN-S. SARAVANAN-M. VINOD-R.: "Eudragit NE30D Based Metformin/Gliclazide Extended Release Tablets: Formulation, characterisation and in Vitro Release Studies" CHEM. PHARM. BULL., vol. 50, no. 11, November 2002 (2002-11), pages 1495-1498, XP001207838 abstract table 1 page 1495	1-8, 10-16, 18-20

INTERNATIONAL SEARCH REPORT

national application No.
PCT/IB2005/002753

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 claims 18,19 are 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/IB2005/002753

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		AU 749550 B2 27-06-2002	
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		DE 69918310 D1 29-07-2004	
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US 2003219482	A1	27-11-2003	NONE