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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 September 2009 (11.09.2009)

PCT

(10) International Publication Number
WO 2009/111200 A1

(51) **International Patent Classification**:
A01N 37/52 (2006.01) *A61K 9/22* (2006.01)
A61K 31/155 (2006.01)

(21) **International Application Number**:
PCT/US2009/034851

(22) **International Filing Date**:
23 February 2009 (23.02.2009)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/068,016 4 March 2008 (04.03.2008) US

(71) **Applicant** *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(72) **Inventor; and**
(75) **Inventor/Applicant** *(for US only)*: **POURKAVOOS, Nazaneen** [CA/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(74) **Common Representative**: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(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, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, 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, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

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

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

(54) **Title**: PHARMACEUTICAL COMPOSITIONS OF A COMBINATION OF METFORMIN AND A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

(57) **Abstract**: Disclosed are pharmaceutical compositions comprising fixed-dose combinations of an extended-release form of metformin, or a pharmaceutically acceptable salt thereof, coated with an immediate-release form of the DPP-4 inhibitor sitagliptin,

WO 2009/111200 A1

TITLE OF THE INVENTION

PHARMACEUTICAL COMPOSITIONS OF A COMBINATION OF METFORMIN AND A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

BACKGROUND OF THE INVENTION

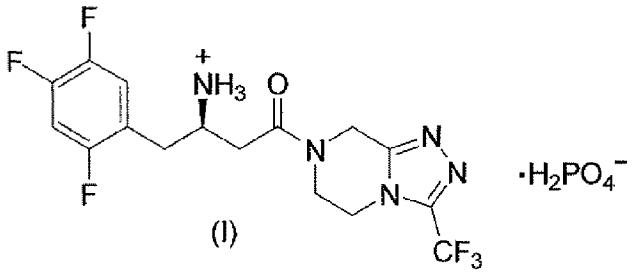
Type 2 diabetes is a chronic and progressive disease arising from a complex pathophysiology involving the dual endocrine defects of insulin resistance and impaired insulin secretion. The treatment of Type 2 diabetes typically begins with diet and exercise, followed by oral antidiabetic monotherapy. For many patients, these regimens do not sufficiently control glycemia during long-term treatment, leading to a requirement for combination therapy within several years following diagnosis. However, co-prescription of two or more oral antidiabetic drugs may result in treatment regimens that are complex and difficult for many patients to follow. Combining two or more oral antidiabetic agents into a single tablet provides a potential means of delivering combination therapy without adding to the complexity of patients' daily regimens. Such formulations have been well accepted in other disease indications, such as hypertension (HYZAAR® which is a combination of losartan potassium and hydrochlorothiazide) and cholesterol lowering (VYTORIN® which is a combination of simvastatin and ezetimibe). The selection of effective and well-tolerated treatments is a key step in the design of a combination tablet. Moreover, it is essential that the components have complementary mechanisms of action and compatible pharmacokinetic profiles. Examples of marketed combination tablets containing two oral antidiabetic agents include Glucovance® (metformin and glyburide), Avandamet® (metformin and rosiglitazone), and Metaglip® (metformin and glipizide).

Metformin represents the only oral antidiabetic agent proven to reduce the total burden of microvascular and macrovascular diabetic complications and to prolong the lives of Type 2 diabetic patients. Furthermore, metformin treatment is often associated with reductions in body weight in overweight patients and with improvements in lipid profiles in dyslipidemic patients. Metformin hydrochloride is marketed in the U.S. and elsewhere as either immediate-release or extended-release formulations with tablet dosage strengths of 500, 750, 850, and 1000 milligrams. Extended-release formulations of metformin have advantages over immediate-release in terms of affording a more uniform maintenance of blood plasma active drug concentrations and providing better patient compliance by reducing the frequency of administration required.

Dipeptidyl peptidase-IV (DPP-4) inhibitors represent a new class of agents that are being developed for the treatment or improvement in glycemic control in patients with Type 2 diabetes. Specific DPP-4 inhibitors either already approved for marketing or under clinical development for the treatment of Type 2 diabetes include sitagliptin, vildagliptin, saxagliptin,

melogliptin, P93/01 (Prosidion), alogliptin, denagliptin, Roche 0730699, TS021 (Taisho), and E3024 (Eisai). For example, oral administration of sitagliptin, vildagliptin, alogliptin, and saxagliptin to human Type 2 diabetics has been found to reduce fasting glucose and postprandial glucose excursion in association with significantly reduced HbA_{1c} levels. For reviews on the application of DPP-4 inhibitors for the treatment of Type 2 diabetes, reference is made to the following publications: (1) A.H. Stonehouse, et al., "Management of Type 2 diabetes: the role of incretin mimetics, Exp. Opin. Pharmacother., 7: 2095-2105 (2006); (2) B.D. Green, et al., "Inhibition of dipeptidyl peptidase-IV activity as a therapy of Type 2 diabetes," Exp. Opin. Emerging Drugs, 11: 525-539 (2006); (3) M.M.J. Combettes, "GLP-1 and Type 2 diabetes: physiology and new clinical advances," Curr. Opin. Pharmacol., 6: 598-605 (2006); and R.K. Campbell, "Rationale for Dipeptidyl Peptidase 4 Inhibitors: A New Class of Oral Agents for the Treatment of Type 2 Diabetes Mellitus," Ann. Pharmacother., 41: 51-60 (2007).

Sitagliptin phosphate having structural formula I below is the dihydrogenphosphate salt of (2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine.



(I)

In one embodiment sitagliptin phosphate is in the form of a crystalline monohydrate. Sitagliptin free base and pharmaceutically acceptable salts thereof are disclosed in U.S. Patent No. 6,699,871, the contents of which are hereby incorporated by reference in their entirety. Crystalline sitagliptin phosphate monohydrate is disclosed in U.S. Patent No. 7,326,708, the contents of which are hereby incorporated by reference in their entirety. Sitagliptin phosphate has been approved for marketing in several countries, including the U.S., Europe, Canada, and Mexico, for the treatment of Type 2 diabetes and is branded as JANUVIA® in the U.S. and elsewhere. For reviews, see D. Drucker, et al., "Sitagliptin," Nature Reviews Drug Discovery, 6: 109-110 (2007); C.F. Deacon, "Dipeptidyl peptidase 4 inhibition with sitagliptin: a new therapy for Type 2 diabetes," Exp. Opin. Invest. Drugs, 16: 533-545 (2007); K.A. Lyseng-Williamson, "Sitagliptin," Drugs, 67: 587-597 (2007); and B. Gallwitz, "Sitagliptin: Profile of a Novel DPP-4 Inhibitor for the Treatment of Type 2 Diabetes (Update)," Drugs of Today, 43: 801-814 (2007).

The combination of sitagliptin and metformin provides substantial and additive glycemic improvement in patients with Type 2 diabetes (B.J. Goldstein, et al., "Effect of Initial Combination Therapy with Sitagliptin, a DPP-4 Inhibitor, and Metformin on Glycemic Control

in Patients with Type 2 Diabetes," Diabetes Care, 30: 1979-1987 (2007) and B. Gallwitz, "Sitagliptin with Metformin: Profile of a combination for the treatment of Type 2 diabetes," Drugs of Today, 43: 681-689 (2007). A fixed-dose combination of immediate-release of both metformin and sitagliptin has been approved for marketing in several countries, including U.S. and Mexico, for adult patients with Type 2 diabetes who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin. The combination is branded as JANUMET® in the U.S. JANUMET® tablets contain 50 mg sitagliptin and either 500, 850, or 1000 mg metformin. Pharmaceutical compositions comprising fixed-dose combinations of immediate-release sitagliptin and immediate-release metformin are disclosed in PCT international patent application WO 2007/078726 which published on July 12, 2007.

Extended-release formulations of metformin are disclosed in US 6,340,475; US 6,635,280; US 6,866,866; US 6,475,521; and US 6,660,300. Pharmaceutical formulations containing extended-release metformin and a thiazolidinedione antihyperglycemic agent are described in WO 2004/026241 (1 April 2004) and WO 2006/107528 (12 October 2006). Pharmaceutical compositions comprising a DPP-4 inhibitor and a slow-release form of metformin are disclosed in US 2007/0172525 (26 July 2007). Stable pharmaceutical compositions of an immediate-release form of the antihyperglycemic sulfonylurea glimepiride and extended-release metformin are disclosed in US 2007/0264331 (15 November 2007).

The present invention provides for pharmaceutical compositions comprising a core tablet formulation of a fixed-amount of metformin that is coated with a sustained-release (SR) polymer film which is further coated with an immediate release form of a fixed amount of sitagliptin. The metformin core tablet is prepared by wet or dry processing methods prior to coating with the SR polymer composition.

The present invention also provides processes to prepare pharmaceutical compositions of a fixed-dose combination of immediate-release sitagliptin and extended-release metformin by wet or dry processing methods. The wet processing methods include wet granulation.

Another aspect of the present invention provides methods for the treatment of Type 2 diabetes by administering to a host in need of such treatment a therapeutically effective amount of a pharmaceutical composition of the present invention.

These and other aspects of the invention will become readily apparent from the detailed description which follows.

SUMMARY OF THE INVENTION

The present invention is directed to novel pharmaceutical compositions comprising a core tablet formulation of metformin, or a pharmaceutically acceptable salt thereof,

coated with a sustained-release polymer film which is further coated with an immediate-release form of the DPP-4 inhibitor sitagliptin, or a pharmaceutically acceptable salt thereof, processes for preparing such compositions, and methods of treating Type 2 diabetes with such compositions. In particular, the invention is directed to pharmaceutical compositions comprising a core tablet formulation of metformin hydrochloride coated with a sustained-release polymer film which is further coated with an immediate-release form of sitagliptin phosphate.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a graph showing *in vitro* metformin dissolution profiles of an immediate-release (IR) 1000-mg metformin hydrochloride core tablet coated with cellulose acetate sustained-release polymer film compositions of varying porosity with 3, 5, or 7 weight percent gain relative to the core tablet weight.

FIG. 2 is a graph comparing *in vitro* metformin dissolution profiles of an immediate-release (IR) 500-mg metformin hydrochloride tablet with metformin dissolution profiles of an immediate-release (IR) 1000-mg metformin hydrochloride core tablet coated with a high porosity cellulose acetate sustained-release polymer film composition with 3, 5, or 7 weight percent gain relative to the core tablet weight.

FIG. 3 is a graph comparing *in vitro* metformin dissolution profiles of an immediate-release (IR) 500-mg metformin hydrochloride tablet with metformin dissolution profiles of a 1000-mg immediate-release (IR) metformin hydrochloride core tablet coated with a "modified high porosity" cellulose acetate sustained-release polymer film composition with 3, 5, or 7 weight percent gain relative to the core tablet weight.

FIG. 4 is a graph showing *in vitro* dissolution profiles for sitagliptin phosphate from the drug film layer in a pharmaceutical composition of the present invention compared to sitagliptin phosphate in JANUMET™ which is a marketed fixed-dose combination of immediate-release metformin hydrochloride and immediate-release sitagliptin phosphate.

DETAILED DESCRIPTION OF THE INVENTION

One aspect of the present invention is directed to pharmaceutical compositions comprising a core tablet formulation of a fixed-amount of metformin, or a pharmaceutically acceptable salt thereof, which core tablet is coated with a sustained-release polymer film which is further coated with an immediate release form of a fixed amount of the DPP-4 inhibitor sitagliptin, or a pharmaceutically acceptable salt thereof.

A preferred pharmaceutically acceptable salt of sitagliptin is the dihydrogenphosphate salt of structural formula I above (sitagliptin phosphate). A preferred form of the dihydrogenphosphate salt is the crystalline monohydrate disclosed in U.S. Patent No. 7,326,708, the contents of which are hereby incorporated by reference in their entirety.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.