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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 January 2013 (03.01.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/001457 Al

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61P 3/10* (2006.01)
A61K 31/4985 (2006.01)

(21) International Application Number:
PCT/IB2012/053234

(22) International Filing Date:
26 June 2012 (26.06.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1867/DEL/201 1 30 June 201 1 (30.06.201 1) IN
2323/DEL/201 1 16 August 201 1 (16.08.201 1) IN

(71) Applicant *(for all designated States except US):* **RANBAXY LABORATORIES LIMITED** [IN/IN]; Head Office: 12th Floor, Devika Tower, 06 Nehru Place, New Delhi, Delhi 110019 (IN).

(72) Inventors; and
(75) Inventors/Applicants *(for US only):* **JAYACHANDRA, Suresh, Babu** [IN/IN]; C-237, Phase - I, Sushant Lok, Gurgaon, Haryana 122001 (IN). **SHAH, Jigar, Bhaskarbhai** [IN/IN]; B-753, Tumdi Street, Sonari Mahal, Bharuch, Gujarat 392001 (IN). **CHIGURU, Sailu** [IN/IN]; s/o Laxman CHIGURU, Post & Village Kondapoor, Musthabad, Karimnager, Andhra Pradesh 505303 (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED;** c/o Dr. B. Vijayaraghavan, Intellectual Property Dept., 600 College Road East, Suite 2100, Princeton, New Jersey 08540 (US).

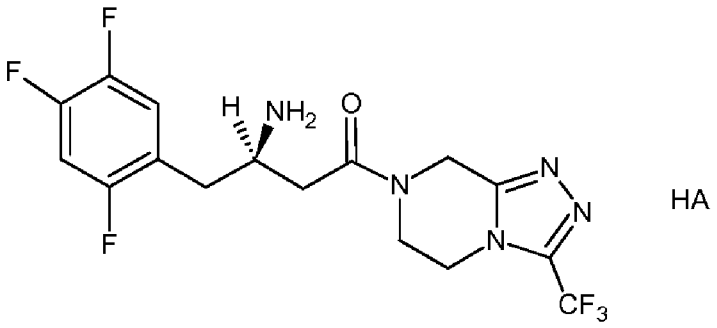
(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

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

(54) **Title:** NOVEL SALTS OF SITAGLIPTIN



Formula 1

(57) **Abstract:** The present invention provides sitagliptin 4-methylsalicylate, sitagliptin myristate, sitagliptin isophthalate, sitagliptin isonicotinide, sitagliptin adipate, their polymorphic form, processes for their preparation and pharmaceutical compositions thereof.

WO 2013/001457 A1

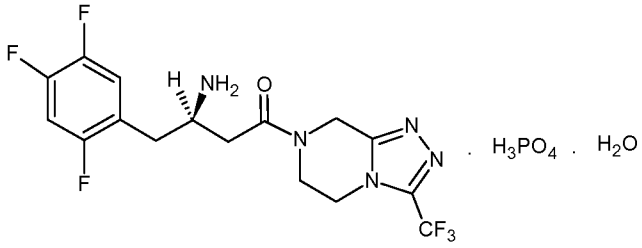
NOVEL SALTS OF SITAGLIPTIN

Field of the Invention

The present invention provides novel salts of sitagliptin, its polymorphic form, processes for their preparation and pharmaceutical compositions thereof.

Background of the Invention

Sitagliptin dihydrogen phosphate monohydrate of Formula A, an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme, chemically designated as 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.



Formula A

U.S. Patent No. 6,699,871 (hereinafter "the '871 patent"), in particular Example 7, provides a process for the preparation of sitagliptin base and its hydrochloride salt. A list of pharmaceutically acceptable salts is generally included in the '871 patent.

U.S. Patent No. 7,326,708 provides a process for the preparation of sitagliptin dihydrogen phosphate monohydrate.

PCT Publication WO 2005/072530 provides a process for the preparation of crystalline salts of sitagliptin with hydrochloric acid, benzene sulfonic acid, /^-toluene sulfonic acid, D- and L-tartaric acid and (1S)-(+)- and (1R)-(-)- 10-camphorsulfonic acid.

PCT Publication WO 2005/030127 (hereinafter "PCT 127") provides a process for the preparation of sitagliptin dihydrogen phosphate anhydrate Form IV which involves heating sitagliptin dihydrogen phosphate monohydrate at 120°C for about 2 hours or by heating the sitagliptin dihydrogen phosphate monohydrate above 58°C for about 8 hours.

PCT '127 also provides a process for the preparation of sitagliptin dihydrogen phosphate anhydrate Form I by heating sitagliptin dihydrogen phosphate anhydrate Form IV at a temperature above 140°C for about 1 hour. According to this publication, Form IV is metastable and converts to the crystalline monohydrate slowly under ambient conditions and rapidly under high relative humidity (98%) at room temperature.

PCT Publication WO 2005/020920 provides a process for the preparation of crystalline anhydrate Form I, crystalline desolvated anhydrate Form II, crystalline anhydrate Form III, crystalline ethanol solvate of sitagliptin dihydrogen phosphate. It also provides a process for the preparation of mixture of sitagliptin dihydrogen phosphate anhydrate Form I and anhydrate Form III.

PCT Publication WO 2006/033848 provides a process for the preparation of crystalline sitagliptin dihydrogen phosphate monohydrate and amorphous sitagliptin dihydrogen phosphate.

PCT Publication WO 2007/035198 provides a process for the preparation of dodecylsulfate salt of sitagliptin.

PCT Publication WO 2008/000418 provides a process for the preparation of anhydrous sitagliptin hydrochloride in amorphous form.

PCT Publication WO 2009/120746 provides processes for the preparation of crystalline form of sitagliptin phosphate, characterized by a powder XRD pattern with peaks at about 4.7, 13.5, 17.7, 18.3, and 23.7 ±0.2° 2Θand sitagliptin phosphate Form II.

U.S. Publication 2009/247532 provides processes for the preparation of polymorph Form V of crystalline sitagliptin phosphate and polymorph Form I of sitagliptin phosphate.

PCT Publication WO 2009/084024 provides a process for the preparation of R-sitagliptin dibenzyl-L-tartrate.

PCT Publication WO 2009/085990 provides a process for the preparation of crystalline anhydrate Form A of the dihydrogen phosphate salt of sitagliptin, crystalline sitagliptin sulfate, crystalline sitagliptin hydrobromide, crystalline sitagliptin methane sulfonate, crystalline sitagliptin acetate, crystalline sitagliptin benzoate, crystalline sitagliptin oxalate, crystalline sitagliptin succinate, crystalline sitagliptin mandelate, crystalline sitagliptin fumarate and crystalline sitagliptin lactate.

PCT Publication WO 2010/032264 provides a process for the preparation of crystalline Form 3 of sitagliptin, crystalline form of dibenzoyl-L-tartaric acid salt of sitagliptin, amorphous form of sitagliptin and anhydrous and hydrated crystalline form of phosphate salt of sitagliptin.

PCT Publication 2010/000469 provides a process for the preparation of sitagliptin hydrochloride Form I, sitagliptin hydrochloride Form II, sitagliptin fumarate Form I, sitagliptin fumarate Form II, sitagliptin malate, sitagliptin sulfate Form I, sitagliptin sulfate Form II, sitagliptin phosphate, sitagliptin succinate Form I and Form II, sitagliptin succinate Form III, sitagliptin lactate, sitagliptin glycolate, sitagliptin maleate Form I, sitagliptin maleate Form II, sitagliptin citrate, amorphous sitagliptin citrate, sitagliptin mesylate Form I and sitagliptin mesylate Form II.

PCT Publication WO 2010/012781 provides a process for the preparation of sitagliptin galactarate, sitagliptin hemi-L-malate, sitagliptin D-gluconate, sitagliptin succinate, sitagliptin hydrobromide, sitagliptin thiocyanate, sitagliptin oxalate, sitagliptin aspartate, sitagliptin ethanedisulfonate, sitagliptin pyroglutamate, sitagliptin glutarate, sitagliptin acetate, sitagliptin hydrochloride amorphous form, sitagliptin citrate amorphous form, sitagliptin hemicitrate amorphous form, sitagliptin glycolate amorphous form and sitagliptin malate amorphous form.

PCT Publication WO 2010/1 17738 provides a process for the preparation of crystalline Form S1 of sitagliptin sulfate, crystalline Form S2 of sitagliptin sulfate, crystalline Form S3 of sitagliptin sulfate, crystalline Form S4 of sitagliptin sulfate, crystalline Form S5 of sitagliptin sulfate, crystalline Form S6 of sitagliptin sulfate, crystalline Form S7 of sitagliptin sulfate, crystalline Form S8 of sitagliptin sulfate, crystalline Form D1 of sitagliptin (+)-dibenzoyl-tartrate, crystalline Form D2 of sitagliptin (+)-dibenzoyl-tartrate, crystalline Form F1 of sitagliptin fumarate, crystalline Form F2 of sitagliptin fumarate, crystalline Form M1 of sitagliptin (D)-(+)-malate, crystalline Form M2 of sitagliptin (D)-(+)-malate, crystalline Form I1 of sitagliptin L-malate, crystalline Form 0 1 of sitagliptin oxalate, crystalline Form 0 2 of sitagliptin oxalate, crystalline Form Q1 of sitagliptin quinate, crystalline Form U1 of sitagliptin succinate, crystalline Form E1 of sitagliptin acetate, crystalline Form A1 of sitagliptin maleate, crystalline Form N1 of sitagliptin (S)-mandelate, crystalline Form N2 of sitagliptin (S)-mandelate, crystalline Form N3 of sitagliptin (S)-mandelate, crystalline Form N4 of sitagliptin (S)-mandelate,

amorphous sitagliptin mandelate, crystalline Form N5 of sitagliptin (R)-mandelate, crystalline FormN6 of sitagliptin (R)-mandelate, crystalline Form L I of sitagliptin lactate, crystalline Form L2 of sitagliptin lactate, crystalline Form L3 of sitagliptin lactate, crystalline Form L4 of sitagliptin lactate and amorphous sitagliptin orotate.

PCT Publication WO 2010/092090 provides a process for the preparation of crystalline sitagliptin D-glucuronate, crystalline sitagliptin glutarate, crystalline sitagliptin hydrogen sulfate, crystalline sitagliptin L-lactate, crystalline sitagliptin oxalate, sitagliptin caprate, sitagliptin L-mandelate, crystals of sitagliptin ethanesulfonate.

PCT Publication WO 2010/122578 provides a process for the preparation of sitagliptin hydrogen phosphate monohydrate and sitagliptin mandalate.

PCT Publication WO 201 1/025932 provides a process for the preparation of sitagliptin phosphate and sitagliptin hydrochloride.

PCT Publication WO 201 1/060213 provides a process for the preparation of sitagliptin phosphate, sitagliptin formate and sitagliptin acetate.

PCT Publication WO 201 1/018494 provides a process for the preparation of sitagliptin fumarate.

Journal of Medicinal Chemistry, 48(1), p. 141-151 (2005) provides a process for the preparation of sitagliptin hydrochloride and sitagliptin fumarate.

Several processes are known in the literature for making sitagliptin or a salt thereof, for example, PCT Publications WO 201 1/049344, WO 2010/131025, WO 2010/078440, WO 2004/083212, WO 2006/065826, WO 2010/097420, WO 2004/080958, WO 2004/087650 and WO 2004/085661.

In the pharmaceutical industry, there is a constant need to identify the critical physicochemical parameters such as novel salts, novel polymorphic forms that affect the drug's performance, stability, etc., which may play a key role in determining a drug's market acceptance and success.

Since sitagliptin is an important therapeutic agent, developing other, hitherto unknown salts is of value to pharmaceutical science, especially in terms of having improved solubility, stability, excellent storage and handling stabilities, bioavailability, etc.

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.