

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/353, 31/4439, 9/32, 9/52, 45/06, A61P 3/10	A1	(11) International Publication Number: WO 00/28989 (43) International Publication Date: 25 May 2000 (25.05.00)																	
(21) International Application Number: PCT/EP99/08704 (22) International Filing Date: 8 November 1999 (08.11.99) (30) Priority Data: <table border="0"> <tr> <td>9824866.9</td> <td>12 November 1998 (12.11.98)</td> <td>GB</td> </tr> <tr> <td>9824867.7</td> <td>12 November 1998 (12.11.98)</td> <td>GB</td> </tr> <tr> <td>9824869.3</td> <td>12 November 1998 (12.11.98)</td> <td>GB</td> </tr> <tr> <td>9912193.1</td> <td>25 May 1999 (25.05.99)</td> <td>GB</td> </tr> <tr> <td>9912190.7</td> <td>25 May 1999 (25.05.99)</td> <td>GB</td> </tr> <tr> <td>9912191.5</td> <td>25 May 1999 (25.05.99)</td> <td>GB</td> </tr> </table> (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): LEWIS, Karen [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). LILLIOTT, Nicola, Jayne [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). MACKENZIE, Donald, Colin [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).	9824866.9	12 November 1998 (12.11.98)	GB	9824867.7	12 November 1998 (12.11.98)	GB	9824869.3	12 November 1998 (12.11.98)	GB	9912193.1	25 May 1999 (25.05.99)	GB	9912190.7	25 May 1999 (25.05.99)	GB	9912191.5	25 May 1999 (25.05.99)	GB	RE, Vincenzo [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). (74) Agent: RUTTER, Keith; SmithKline Beecham Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
9824866.9	12 November 1998 (12.11.98)	GB																	
9824867.7	12 November 1998 (12.11.98)	GB																	
9824869.3	12 November 1998 (12.11.98)	GB																	
9912193.1	25 May 1999 (25.05.99)	GB																	
9912190.7	25 May 1999 (25.05.99)	GB																	
9912191.5	25 May 1999 (25.05.99)	GB																	
(54) Title: PHARMACEUTICAL COMPOSITION FOR MODIFIED RELEASE OF AN INSULIN SENSITISER AND ANOTHER ANTIDIABETIC AGENT																			
(57) Abstract <p>A pharmaceutical composition, which composition comprises: an insulin sensitiser and another antidiabetic agent and a pharmaceutically acceptable carrier therefor, wherein the composition is arranged to provide a modified release of at least one of the insulin sensitiser and the other antidiabetes agent, and the use of such composition in medicine.</p>																			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

This invention relates to a novel composition, in particular to a modified release composition and its use in medicine, especially its use for the treatment of diabetes mellitus, preferably Type 2 diabetes, and conditions associated with diabetes mellitus.

Alpha glucosidase inhibitor antihyperglycaemic agents (or alpha glucosidase inhibitors) and biguanide antihyperglycaemic agents (or biguanides) are commonly used in the treatment of Type 2 diabetes. Acarbose, voglibose, emiglitate and miglitol are examples of alpha glucosidase inhibitors. 1,1 - Dimethylbiguanidine (or metformin) is a particular example of a biguanide.

Insulin secretagogues are compounds that promote increased secretion of insulin by the pancreatic beta cells. The sulphonylureas are well known examples of insulin secretagogues. The sulphonylureas act as hypoglycaemic agents and are used in the treatment of Type 2 diabetes. Examples of sulphonylureas include glibenclamide (or glyburide), glipizide, gliclazide, glimepiride, tolazamide and tolbutamide.

European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter 'Compound (I)'). WO94/05659 discloses certain salts of Compound (I) including the maleate salt at example 1 thereof.

Compound (I) is an example of a class of anti-hyperglycaemic agents known as 'insulin sensitisers'. In particular Compound (I) is a thiazolidinedione insulin sensitiser.

European Patent Applications, Publication Numbers: 0008203, 0139421, 0032128, 0428312, 0489663, 0155845, 0257781, 0208420, 0177353, 0319189, 0332331, 0332332, 0528734, 0508740; International Patent Application, Publication Numbers 92/18501, 93/02079, 93/22445 and United States Patent Numbers 5104888 and 5478852, also disclose certain thiazolidinedione insulin sensitisers.

Another series of compounds generally recognised as having insulin sensitiser activity are those typified by the compounds disclosed in International Patent Applications, Publication Numbers WO93/21166 and WO94/01420. These compounds are herein referred to as 'acyclic insulin sensitisers'. Other examples of acyclic insulin sensitisers are those disclosed in United States Patent Number 5232945 and International Patent Applications, Publication Numbers WO92/03425 and WO91/19702.

Examples of other insulin sensitisers are those disclosed in European Patent Application, Publication Number 0533933, Japanese Patent Application Publication Number 05271204 and United States Patent Number 5264451.

The above mentioned publications are incorporated herein by reference.

It is now indicated that certain modified release pharmaceutical compositions allow administration of a single daily dose of Compound (I) and another antidiabetic agent, such as an alpha glucosidase inhibitor, a biguanide or an insulin secretagogue, to provide an advantageous delivery of drug for maintaining effective glycaemic control with no observed adverse side effects. Such modified release is therefore considered to be particularly useful for the delivery of insulin sensitisers in combination with other antidiabetic agents for the treatment of diabetes mellitus, especially Type 2 diabetes and conditions associated with diabetes mellitus.

Accordingly, the invention provides a pharmaceutical composition, suitable for the treatment of diabetes mellitus, especially Type 2 diabetes and conditions associated with diabetes mellitus in a mammal, such as a human, which composition comprises: an insulin sensitiser, such as Compound (I), and another antidiabetic agent, such as an alpha glucosidase inhibitor, a biguanide or an insulin secretagogue, and a pharmaceutically acceptable carrier therefor, wherein the composition is arranged to provide a modified release of at least one of the insulin sensitiser and the other antidiabetic agent.

In another aspect, the invention provides a modified release pharmaceutical composition, suitable for the treatment of diabetes mellitus, especially Type 2 diabetes and conditions associated with diabetes mellitus in a mammal, such as a human, which composition comprises: an insulin sensitiser, such as Compound (I), and another antidiabetic agent, such as an alpha glucosidase inhibitor, a biguanide or an insulin secretagogue, and a pharmaceutically acceptable carrier therefor, wherein the carrier is arranged to provide a modified release of at least one of the insulin sensitiser and the other antidiabetic agent

Suitably, the release of both the insulin sensitiser and the other antidiabetic agent is modified.

However, it is envisaged that the release of only the insulin sensitiser is modified. It is also envisaged that the release of only the other antidiabetic agent is modified. The remaining active agent would of course be subject to non-modified release.

Suitably, the modified release is delayed, pulsed or sustained release.

In one aspect the modified release is a delayed release.

Delayed release is conveniently obtained by use of a gastric resistant formulation such as an enteric formulation, such as a tablet coated with a gastric resistant polymer, for example Eudragit L100-55. Other gastric resistant polymers include methacrylates, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phtahlate, in particular, Aquateric, Sureteric, HPMCP-HP-55S.

The enteric coated tablet may be a single layer tablet, where the active agents are admixed prior to compression into tablet form, or a multi-layer tablet, such as a bi-or tri-layer tablet, wherein each active agent is present in a discrete layer within the compressed

tablet form. The discrete table layers can be arranged as required to provide modified or non-modified release of each active agent.

In a further aspect the modified release is a sustained release, for example providing effective release of active agents over a time period of up to 26 hours, typically
5 in the range of 4 to 24 hours.

Sustained release is typically provided by use of a sustained release matrix, usually in tablet form, such as disintegrating, non-disintegrating or eroding matrices.

Sustained release is suitably obtained by use of a non disintegrating matrix tablet formulation, for example by incorporating Eudragit RS into the tablet. Alternative non
10 disintegrating matrix tablet formulations are provided by incorporating methacrylates, cellulose acetates, hydroxypropyl methylcellulose phtahlate, in particular Eudragit L and RL , Carbopol 971P, HPMCP-HP-55S into the tablet.

Sustained release is further obtained by use of a disintegrating matrix tablet formulation, for example by incorporating methacrylates, methylcellulose, in particular
15 Eudragit L, Methocel K4M into the tablet.

Sustained release can also be achieved by using a semi-permeable membrane coated tablet for example by applying methacrylates, ethylcellulose, cellulose acetate, in particular Eudragit RS, Surelease to the tablet.

Sustained release can also be achieved by using a multi layer tablet, where each
20 active ingredient is formulated together or as a separate layer, for example as a matrix tablet, with the other layers providing further control for sustained release of either one or both active agents.

In yet a further aspect the modified release is a pulsed release, for example providing up to 4, for example 2, pulses of active agent per 24 hours.

25 One form of pulsed release is a combination of non-modified release of active agent and delayed release.

Suitable modified release includes controlled release. The composition of the invention also envisages a combination of pulsed, delayed and/or sustained release for each of the active agents, thereby enabling for example the release of the reagents at
30 different times. For example, where the composition comprises an insulin sensitiser and a biguanide, such as metformin, the composition can be arranged to release the metformin overnight.

A suitable alpha glucosidase inhibitor is acarbose.

Other suitable alpha glucosidase inhibitors are emiglitate and miglitol. A further
35 suitable alpha glucosidase inhibitor is voglibose.

Suitable biguanides include metformin, buformin or phenformin, especially metformin.

Suitable insulin secretagogues include sulphonylureas.

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.