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(54) Title: TREATMENT OF DIABETES WITH THIAZOLIDINEDIONE, INSULIN SECRETAGOGUE AND BIGUANIDE

(57) Abrégé/Abstract:
A method for the treatment of diabetes mellitus and conditions associated with diabetes mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser, an insulin secretagogue and a biguanide antihyperglycaemic agent, to a mammal in need thereof; and composition for use in such method.

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(54) Title: TREATMENT OF DIABETES WITH THIAZOLIDINEDIONE, INSULIN SECRETAGOGUE AND DIGUANIDE

(57) Abstract

A method for the treatment of diabetes mellitus and conditions associated with diabetes mellitus in a mammal, which method comprises administering an effective non–toxic and pharmaceutically acceptable amount of an insulin sensitiser, an insulin secretagogue and a biguanide antihyperglycaemic agent, to a mammal in need thereof; and composition for use in such method.

TREATMENT OF DIABETES WITH THIAZOLIDINEDIONE, INSULIN SECRETAGOGUE AND BIGUANIDE

This invention relates to the treatment of diabetes mellitus, especially non-insulin dependent diabetes (NIDDM) (or Type 2 diabetes) and conditions associated with diabetes mellitus.

Insulin secretagogues are compounds which promote increased secretion of insulin by the pancreatic beta cells.

The sulphonylureas are well known examples of insulin secretagogues. The sulphonylureas act as antihyperglycaemic agents and are used in the treatment of Type 2 diabetes. Examples of sulphonylureas include glibenclamide, glipizide, gliclazide, glimepiride, tolazamide and tolbutamide.

Biguanide antihyperglycaemic agents are commonly used in the treatment of Type 2 diabetes. 1,1-Dimethylbiguanidine (or Metformin) is an example of a biguanide antihyperglycaemic agent.

European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and antihyperlipidaemic 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)"). WO 94/05659 discloses certain salts of Compound (I) including the maleate salt.

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.

It is now surprisingly indicated that a specific dosage of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof in combination with glimepiride and a biguanide antihyperglycaemic agent provides a particularly beneficial effect on glycaemic control. Such a combination is therefore particularly useful for the treatment of diabetes mellitus, especially Type 2 diabetes and conditions associated with diabetes mellitus. The treatment is also indicated to proceed with minimum side effects.

Accordingly, the invention provides a combination comprising 2 to 12mg of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof , glimepiride and a biguanide antihyperglycaemic agent.

In the combination compound (I), or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof, the glimepiride and the biguanide antihyperglycaemic agent are formulated either as a single pharmaceutical composition or as separate pharmaceutical compositions.

In another aspect the invention provides the use of 2 to 12 mg of 5-[4-[2-(N-methyl)-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof, glimepiride and a biguanide antihyperglycaemic agent in the manufacture of a medicament for use in the treatment of diabetes mellitus and/or a condition associated with diabetes mellitus

In a further aspect the invention provides the use of 2 to 12 mg of 5-[4-[2-(N-methyl)-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for use with glimepiride and a biguanide antihyperglycaemic agent in the treatment of diabetes mellitus and/or a condition associated with diabetes mellitus.

In a still further aspect the invention provides the use of glimepiride in the manufacture of a medicament for use with 2 to 12 mg of 5-[4-[2-(N-methyl)-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof, and a biguanide

antihyperglycaemic agent in the treatment of diabetes mellitus and/or a condition associated with diabetes mellitus.

In yet another aspect the invention provides the use of a biguanide antihyperglycaemic agent in the manufacture of a medicament for use with 2 to 12 mg of 5-[4-[2-(N-methyl)-N-(2-pyridyl)amino) ethoxy]benzyl]thiazolidine-2,4-dione (Compound I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof, and glimepiride in the treatment of diabetes mellitus and/or a condition associated with diabetes mellitus.

A suitable biguanide antihyperglycaemic agent is metformin, buformin or phenformin, especially metformin.

In accordance with the invention 2 to 12 mg of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof is administered, especially per day.

Particularly, the combination of the invention comprises 2 to 4, 4 to 8 or 8 to 12 mg of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof. Typically this dosage is given per day.

Particularly, the combination of the invention comprises 2 to 4 mg of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof. Typically this dosage is given per day.

Particularly, the combination of the invention comprises 4 to 8 mg of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof. Typically this dosage is given per day.

Particularly, the combination of the invention comprises 8 to 12 mg of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof. Typically this dosage is given per day.

Preferably, the combination of the invention comprises 2 mg of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof. Typically this dosage is given per day.

Preferably, the combination of the invention comprises 4 mg of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof. Typically this dosage is given per day.

Preferably, the combination of the invention comprises 8 mg of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof. Typically this dosage is given per day.

It will be understood that compound (I), the glimepiride and the biguanide antihyperglycaemic agent are each administered in a pharmaceutically acceptable form, including pharmaceutically acceptable derivatives such as pharmaceutically acceptable salts, esters and solvates thereof, as appropriate. In certain instances herein the names used for the biguanide antihyperglycaemic agents may relate to a particular pharmaceutical form of the relevant active agent: It will be understood that all pharmaceutically acceptable forms of the active agents per se are encompassed by this invention.

Suitable pharmaceutically acceptable salted forms of Compound (I) include those described in the above mentioned patents and patent applications such as in EP 0306228 and WO 94/05659. A preferred pharmaceutically acceptable salt for Compound (I) is a maleate.

Suitable pharmaceutically acceptable solvated forms of Compound (I) include those described in the above mentioned patents and patent applications, such as in EP 0306228 and WO 94/05659, in particular hydrates.

Suitable pharmaceutically acceptable forms of the glimepiride and the biguanide antihyperglycaemic agent depend upon the particular compound used but include known pharmaceutically acceptable forms of the particular compound chosen. Such derivatives are found or are referred to in standard reference texts such as British and US Pharmacopoeias, Remington: The Science and Practice of Pharmacy (formerly Remington's Pharmaceutical Sciences) 19th edition, 1995, Mack Publishing Co., Easton PA., Martindale the Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition, 1996, page 341 and pages cited therein).

Compound (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, may be prepared using known methods, for example those disclosed in the above mentioned patents and patent applications, such as EP 0306228 and WO 94/05659.

Compound (I) may exist in one or several tautomeric forms, all of which are encompassed by the term Compound (I) as individual tautomeric forms or as mixtures thereof. Compound (I) contains a chiral carbon atom, and hence can exist in up to two stereoisomeric forms, the term Compound (I) encompasses all of these isomeric forms whether as individual isomers or as mixtures of isomers, including racemates.

The glimepiride and biguanide antihyperglycaemic agent of choice is prepared according to known methods, such methods are found or are referred to in standard reference texts, such as the British and US Pharmacopoeias, Remington (cited above), Martindale The Extra Pharmocopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition, 1996, page 341 and pages cited therein).

When used herein the term "conditions associated with diabetes" includes conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus. Also included in "conditions association with diabetes" are those conditions associated with the pre-diabetic state.

When used herein the term "conditions associated with pre-diabetic state" includes conditions such as insulin resistance, including hereditary insulin resistance, impaired glucose tolerance and hyperinsulinaemia.

"Conditions associated with diabetes mellitus itself" include hyperglycaemia, insulin resistance, including acquired insulin resistance. Further conditions associated with diabetes mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance and gestational diabetes.

"Complications associated with diabetes mellitus" includes renal disease, especially renal disease associated with Type 2 diabetes, neuropathy and retinopathy.

Renal diseases associated with Type 2 diabetes include nephropathy, glomerulonephritis, glomerular sclerosis, hypertensive nephrosclerosis and end stage renal disease. Additional renal diseases associated with Type 2 diabetes include nephrotic syndrome.

For the avoidance of doubt, when reference is made herein to scalar amounts, including mg amounts, of Compound (I) in a pharmaceutically acceptable form, the scalar amount referred to is made in respect of Compound (I) *per se*. For example 2 mg of Compound (I) in the form of the maleate salt is that amount of maleate salt which contains 2 mg of Compound (I).

Diabetes mellitus is preferably Type 2 diabetes.

The particularly beneficial effect of glycaemic control provided by the treatment of the invention is indicated to be a synergistic effect relative to the control expected for the sum of the effects of the individual active agents.

Suitably Compound (I) is the agent of first administration. Glycaemic control may be characterised using conventional methods, for example by measurement of a typically used index of glycaemic control such as fasting plasma glucose or glycosylated haemoglobin (HbAlc). Such indices are determined using standard methology, for example those described in: Tuescher A, Richterich, P., Schweiz. med. Wschr.101 (1971), 345 and 390 and Frank P., "Monitoring the Diabetic Patent with Glyscosolated Hemoglobin Measurements", Clinical Products 1988.

In a preferred aspect, the dosage level of each of the active agents when used

in accordance with the treatment of the invention will be less than would have been required from a purely additive effect upon glycaemic control.

There is also an indication that the treatment of the invention will effect an improvement, relative to the individual agents, in the levels of advanced glycosylation end products (AGEs), leptin and serum lipids including total cholesterol, HDL-cholesterol, LDL-cholesterol including improvements in the ratios thereof, in particular an improvement in serum lipids including total cholesterol, HDL-cholesterol, LDL-cholesterol including improvements in the ratios thereof.

As used herein the term "pharmaceutically acceptable" embraces both human and veterinary use: for example the term "pharmaceutically acceptable" embraces a veterinarily acceptable compound.

In the present invention, the active medicaments are preferably administered in pharmaceutical composition form. As indicated above, such compositions can include all medicaments or one only of the medicaments.

Accordingly, in one aspect of the invention also provides a pharmaceutical composition comprising 2 to 12 mg of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof, glimepiride and a biguanide antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor.

Such compositions may be prepared by admixing 2 to 12 mg of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof, glimepiride and a biguanide antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor.

Usually the compositions are adapted for oral administration. However, they may be adapted for other modes of administration, for example parenteral administration, sublingual or transdermal administration.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

Unit dose presentation forms for oral administration may be tablets

and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The compositions are preferably in a unit dosage form in an amount appropriate for the relevant daily dosage.

Suitable dosages of Compound (I) comprise 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound (I).

In the treatment the medicaments may be administered from 1 to 6 times a day, but most preferably 1 or 2 times pr day.

Particular dosages of Compound (I) are 2 mg/day, 4 mg/day, including 2 mg twice per day, and 8 mg/day, including 4 mg twice per day.

Suitable dosages including unit dosages of the insulin secretagogue, such as the sulphonylurea or the biguanide antihyperglycaemic agent, include the known dosages including unit doses for these compounds as described or referred to in reference text such as the British and US Pharmacopoeias, Remington (cited above), and Martindale, The Extra Pharmacopoeia (cited above).

For sulphonylureas generally, a typical daily dosage of glibenclamide is in the range of from 2.5 to 20 mg, for example 10 mg twice per day or 20 mg one per day; a

typical daily dosage of glipizide is in the range of from 2.5 to 40 mg; a typical daily dosage of gliclazide is in the range of from 40 to 320 mg; a typical daily dosage of tolazamide is in the range of from 100 to 1000 mg; a typical daily dosage of tolbutamide is in the range of from 1000 to 3000 mg; a typical daily dosage of chlorpropamide is in the range of from 100 to 500 mg; and a typical daily dosage of gliquidone is in the range of from 15 to 180 mg.

Repaglinide may be taken in amounts, usually in the range of from 0.5mg to 4mg and usually with meals, up to a typical maximum daily dosage of 16mg per day.

With regard to the biguanide antihyperglycaemic agents, suitable dosages of metformin include up to 3000mg per day, in unit doses of 500mg (for example two or three times per day) or 850mg (for example two times per day), one example of a dosage for metformin is 500mg once building to five times per day.

The solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the Compound (I) is suspended in the vehicle instead of being

dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending upon the method of administration.

Composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

The compositions are prepared and formulated according to conventional methods, such as those disclosed in standard reference texts, for example the British and US Pharmacopoeias, Remington (cited above), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31 st Edition page 341 and pages cited therein) and Harry's Cosmeticology (Leonard Hill Books) for instance 6th Edition, 1973.

In particular, the present invention provides a pharmaceutical composition comprising 2 to 12 mg of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof, glimepiride and a biguanide antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor, for use in the treatment of diabetes mellitus and conditions associated with diabetes mellitus.

A range of 2 to 4 mg includes a range of 2.1 to 4, 2.2 to 4, 2.3 to 4, 2.4 to 4, 2.5 to 4, 2.6 to 4, 2.7 to 4, 2.8 to 4, 2.9 to 4 or 3 to 4.

A range of 4 to 8 mg includes a range of 4.1 to 8, 4.2 to 8, 4.3 to 8, 4.4 to 8, 4.5 to 8, 4.6 to 8, 4.7 to 8, 4.9 to 8, 5 to 8, 6 to 8 or 7 to 8 mg.

A range of 8 to 12 mg includes a range of 8.1 to 12, 8.2 to 12, 8.3 to 12, 8.4 to 12, 8.5 to 12, 8.6 to 12, 8.7 to 12, 8.8 to 12, 8.9 to 12, 9 to 12, 10 to 12 or 11 to 12 mg.

No adverse toxicological effects are expected for the compositions or methods of the invention in the aforementioned dosage ranges.

Composition for compound (I)

Preparation of Concentrate: Tabletting concentrate was prepared using the following materials

Ingredient	Quantity (%)
Milled Compound (I) as maleate salt	13.25 (pure maleate salt)
Sodium Starch Glycollate	5.00
Hydoxypropyl Methylcellulose 2910	5.00
Microcrystalline Cellulose (Avicel PH102)	20.0
Lactose Monohydrate, regular grade	to 100
Purified water	*

* Removed during processing.

The concentrate was then formulated into tablets using the following:

	Quantity (mg per Tablet)			
Tablet Strength	**1.0mg**	**2.0mg**	**4.0mg**	**8.0mg**
Active Ingredient:				
Compound (I) maleate Concentrate granules	10.00	20.00	40.00	80.00
Other Ingredients:				
Sodium Starch Glycollate	6.96	6.46	5.46	10.92
Microcrystalline Cellulose (Avicel PH102)	27.85	25.85	21.85	43.70
Lactose monohydrate, (Pharmatose DCL15),	104.44	96.94	81.94	163.88
Magnesium Stearate	0.75	0.75	0.75	1.50
Total Weight of Tablet Core	150.0	150.0	150.0	300.0
Opadry	4.5	4.5	4.5	9.0
Total Weight of Film Coated Tablet	154.5	154.5	154.5	309.0

Compositions for other active agents are as described in the above mentioned publications.

Claims

1. A combination comprising 2 to 12mg of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof, glimepiride and a biguanide antihyperglycaemic agent.

2. A combination according to claim 1, wherein the biguanide antihyperglycaemic agent is metformin, buformin or phenformin.

3. A combination according to claim 1 or 2, which comprises 2 to 4, 4 to 8 or 8 to 12 mg of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof.

4. A combination according to any one of claims 1 to 3, which comprises 2 to 4 mg of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof.

5. A combination according to any one of claims 1 to 3, which comprises 4 to 8 mg of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof.

6. A combination according to any one of claims 1 to 3, which comprises 8 to 12 mg of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof.

7. A combination according to any one of claims 1 to 3, which comprises 2 mg of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof.

8. A combination according to any one of claims 1 to 3, which comprises 4 mg of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof.

9. A combination according to any one of claims 1 to 3, which comprises 8 mg of Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof.

10. A combination according to any one of claims 1 to 9, wherein Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof, the glimepiride and the biguanide antihyperglycaemic agent are formulated as a single pharmaceutical composition.

11. A combination according to any one of claims 1 to 9, wherein Compound (I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof, the glimepiride and the biguanide antihyperglycaemic agent are formulated as separate pharmaceutical compositions.

12. A pharmaceutical composition comprising a combination as defined in any one of claims 1 to 11 and a pharmaceutically acceptable carrier therefor.

13. Use of 2 to 12 mg of 5-[4-[2-(N-methyl)-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof, glimepiride and a biguanide antihyperglycaemic agent in the manufacture of a medicament for use in the treatment of diabetes mellitus and/or a condition associated with diabetes mellitus.

14. Use of 2 to 12 mg of 5-[4-[2-(N-methyl)-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound I) or a tautomeric

form thereof and/or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for use with glimepiride and a biguanide antihyperglycaemic agent in the treatment of diabetes mellitus and/or a condition associated with diabetes mellitus.

15. Use of glimepiride in the manufacture of a medicament for use with 2 to 12 mg of 5-[4-[2-(N-methyl)-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof, and a biguanide antihyperglycaemic agent in the treatment of diabetes mellitus and/or a condition associated with diabetes millitus.

16. Use of a biguanide antihyperglycaemic agent in the manufacture of a medicament for use with 2 to 12 mg of 5-[4-[2-(N-methyl)-N-(2-pyridyl)amino) ethoxy]benzyl]thiazolidine-2,4-dione (Compound I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof, and glimepiride in the treatment of diabetes mellitus and/or a condition associated with diabetes mellitus.