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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING A PYRAZOLE-O-GLUCOSIDE DERIVATIVE

(57) Abstract: The invention relates to a pharmaceutical composition according to claim 1 comprising a pyrazole-O-glucoside derivative in combination with a DPP IV inhibitor which is suitable in the treatment or prevention of one or more conditions selected from type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance and hyperglycemia. In addition the present invention relates to methods for preventing or treating of metabolic disorders and related conditions.

Pharmaceutical composition comprising a pyrazole-O-glucoside derivative

Technical Field of the Invention

The invention relates to a pharmaceutical composition comprising a pyrazole-O-glucoside derivative of the formula (I) as described hereinafter in combination with a DPP IV inhibitor as specified hereinafter which is suitable in the treatment or prevention of one or more conditions selected from type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance, impaired fasting blood glucose and hyperglycemia.

Furthermore the invention relates to methods

- for preventing, slowing progression of, delaying, or treating a metabolic disorder;
- for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c;
- for preventing, slowing, delaying or reversing progression from impaired glucose tolerance, impaired fasting blood glucose, insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus;
- for preventing, slowing progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus;
- for reducing body weight or preventing an increase in body weight or facilitating a reduction in body weight;
- for preventing or treating the degeneration of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells and/or restoring the functionality of pancreatic insulin secretion;
- for preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of liver fat;
- maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance,

in patients in need thereof characterized in that a pyrazole-O-glucoside derivative of formula (I) as defined hereinafter is administered in combination or alternation with a DPP IV inhibitor as defined hereinafter.

In addition the present invention relates to the use of a pyrazole-O-glucoside derivative of the formula (I) as defined hereinafter for the manufacture of a medicament for use in a method as described hereinbefore and hereinafter.

In addition the present invention relates to the use of a DPP IV inhibitor as defined hereinafter for the manufacture of a medicament for use in a method as described hereinbefore and hereinafter.

The invention also relates to a use of a pharmaceutical composition according to this invention for the manufacture of a medicament for use in a method as described hereinbefore and hereinafter.

Background of the Invention

The patent applications EP 1 213 296, EP 1 338 603 A1, EP 1 354 888, EP 1364 957, EP 1 364 958, EP 1 400 529, EP 1 389 621, WO 03/020737 and the WO 2007/080170 describe novel pyrazole-O-glycoside derivatives. The pyrazole-O-glycoside derivatives are proposed as inducers of urinary sugar excretion and as medicaments in the treatment of diabetes. The European Patent application EP 1 500 403 A1 describes a combination of an inhibitor of renal glucose reabsorption and a hypoglycemic agent. The international patent application WO 2007/014895 describes pyrazole-O-glycoside derivatives as SGLT2 inhibitors and their use in the treatment of metabolic disorders.

Renal filtration and reuptake of glucose contributes, among other mechanisms, to the steady state plasma glucose concentration and can therefore serve as an antidiabetic target. Reuptake of filtered glucose across epithelial cells of the kidney proceeds via sodium-dependent glucose cotransporters (SGLTs) located in the brush-border membranes in the tubuli along the sodium gradient [(1)]. There are at least 3 SGLT isoforms that differ in their expression pattern as well as in their physico-chemical properties [(2)]. SGLT2 is exclusively expressed in the kidney [(3)], whereas SGLT1 is expressed additionally in other tissues like intestine, colon, skeletal and cardiac muscle [(4;5)]. SGLT3 has been found to be a glucose sensor in interstitial cells of the intestine without any transport function [(6)]. Potentially, other related, but not yet characterized genes, may contribute further to renal glucose reuptake [(7, 8, 9)]. Under normoglycemia, glucose is completely reabsorbed by SGLTs in the kidney, whereas the reuptake capacity of the kidney is saturated at glucose concentrations higher than 10mM, resulting in glucosuria ("diabetes mellitus"). This threshold concentration can be decreased by SGLT2-inhibition. It has been shown in experiments with the SGLT inhibitor phlorizin that SGLT-inhibition will partially inhibit the reuptake of glucose from the glomerular filtrate into the blood leading to a decrease in blood glucose concentrations and to glucosuria [(10;11)].

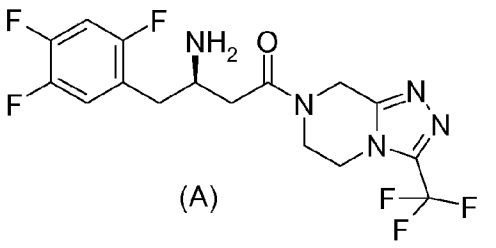
(1) Wright, E.M. (2001) Am. J. Renal Physiol. 280, F10-F18

(2) Wright, E.M. et al. (2004) Pflugers Arch. 447(5):510-8;
(3) You, G. et al. (1995) J. Biol. Chem. 270 (49) 29365-29371;
(4) Pajor AM, Wright EM (1992) J Biol. Chem. 267(6):3557-3560;
(5) Zhou, L. et al. (2003) J. Cell. Biochem. 90:339-346;
(6) Diez-Sampedro, A. et al. (2003) Proc. Natl. Acad. Sci. USA 100(20), 11753-11758;
(7) Tabatabai, N.M. (2003) Kidney Int. 64, 1320-1330;
(8) Curtis, R.A.J. (2003) US Patent Appl. 2003/0054453;
(9) Bruss,M. and Bonisch,H. (2001) Cloning and functional characterization of a new human sugar transporter in kidney (Genbank Acc. No. AJ305237);
(10) Rossetti, L. Et al. (987) J. Clin. Invest. 79, 1510-1515;
(11) Gouvea, W.L. (1989) Kidney Int. 35(4):1041-1048.

DPP IV inhibitors represent a novel class of agents that are being developed for the treatment or improvement in glycemic control in patients with type 2 diabetes.

Specific DPP IV inhibitors currently in clinical trials for the treatment of type 2 diabetes include, for example, the following:

- Sitagliptin (MK-0431) having the structural formula A below is (3*R*)-3-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one, also named (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,

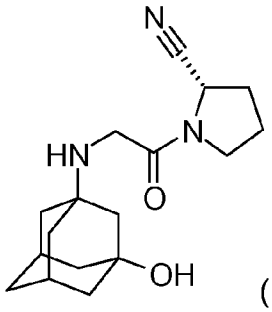


(A)

In one embodiment, sitagliptin is in the form of its dihydrogenphosphate salt, i.e. sitagliptin phosphate. In a further embodiment, sitagliptin phosphate is in the form of a crystalline anhydrate or monohydrate. A class of this embodiment refers to sitagliptin phosphate monohydrate. Sitagliptin free base and pharmaceutically acceptable salts thereof are disclosed in US Patent No. 6,699,871 and in Example 7 of WO 03/004498. Crystalline sitagliptin phosphate monohydrate is disclosed in WO 2005/003135 and in WO 2007/050485. For details, e.g. on a process to manufacture or to formulate this compound or

a salt thereof, reference is thus made to these documents. A tablet formulation for sitagliptin is commercially available under the trade name Januvia®.

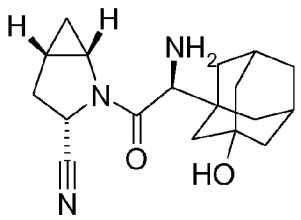
- Vildagliptin (LAF-237) having the structural formula B below is (2S)-{[(3-hydroxyadamantan-1-yl)amino]acetyl}pyrrolidine-2-carbonitrile, also named (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine,



(B)

Vildagliptin is specifically disclosed in US Patent No. 6,166,063 and in Example 1 of WO 00/34241. Specific salts of vildagliptin are disclosed in WO 2007/019255. A crystalline form of vildagliptin as well as a vildagliptin tablet formulation are disclosed in WO 2006/078593. Vildagliptin can be formulated as described in WO 00/34241 or in WO 2005/067976. A modified release vildagliptin formulation is described in WO 2006/135723. For details, e.g. on a process to manufacture or to formulate this compound or a salt thereof, reference is thus made to these documents. A tablet formulation for vildagliptin is expected to be commercially available under the trade name Galvus®.

- Saxagliptin (BMS-477118) having the structural formula C below is (1S,3S,5S)-2-{(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl}-2-azabicyclo[3.1.0]hexane-3-carbonitrile, also named (S)-3-hydroxyadamantylglycine-L-*cis*-4,5-methanoprolinenitrile,



(C)

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