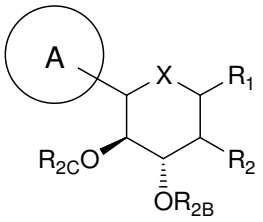
3. SUMMARY

This disclosure is directed, in part, to a method of improving the cardiovascular and/or metabolic health of a patient, which comprises administering to a patient in need thereof a safe and efficacious amount of a dual inhibitor of sodium-glucose cotransporters 1 and 2 ("dual SGLT1/2 inhibitor") that also has a structure of formula I:

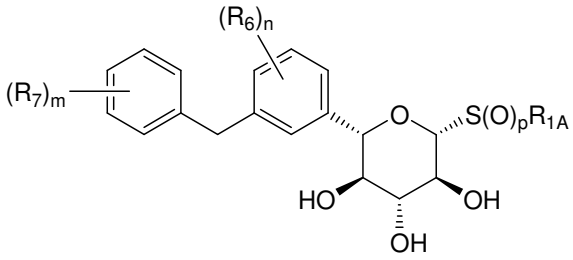


I

or a pharmaceutically acceptable salt thereof, the various substituents of which are defined herein. In a particular example, the patient is concurrently taking another therapeutic agent, such as an anti-diabetic agent, anti-hyperglycemic agent, hypolipidemic/lipid lowering agent, anti-obesity agent, anti-hypertensive agent, or appetite suppressant.

In one example of the disclosure, the administration effects a decrease in the patient's plasma glucose. In one example, the administration effects an improved oral glucose tolerance in the patient. In one example, the administration lowers the patient's post-prandial plasma glucose level. In one example, the administration lowers the patient's plasma fructosamine level. In one example, the administration lowers the patient's HbA1c level. In one example, the administration reduces the patient's blood pressure (*e.g.*, systolic and diastolic). In one example, the administration reduces the patient's triglyceride levels.

In a particular example of the disclosure, the dual SGLT1/2 inhibitor is a compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein: each R_{1A} is independently hydrogen, alkyl, aryl or heterocycle; each R_6 is independently hydrogen, hydroxyl, amino, alkyl, aryl, cyano, halogen, heteroalkyl, heterocycle, nitro, $C{\equiv}CR_{6A}$, OR_{6A}, SR_{6A}, SOR_{6A}, SO_2R_{6A}, $C(O)R_{6A}$, CO_2R_{6A}, CO_2H, $CON(R_{6A})(R_{6A})$, $CONH(R_{6A})$, $CONH_2$, $NHC(O)R_{6A}$, or $NHSO_2R_{6A}$; each R_{6A} is independently alkyl, aryl or heterocycle; each R_7 is independently hydrogen, hydroxyl, amino, alkyl, aryl, cyano, halogen, heteroalkyl, heterocycle, nitro, $C{\equiv}CR_{7A}$, OR_{7A}, SR_{7A}, SOR_{7A}, SO_2R_{7A}, $C(O)R_{7A}$, CO_2R_{7A}, CO_2H, $CON(R_{7A})(R_{7A})$, $CONH(R_{7A})$, $CONH_2$, $NHC(O)R_{7A}$, or $NHSO_2R_{7A}$; each R_{7A} is independently

alkyl, aryl or heterocycle; m is 1-4; n is 1-3; and p is 0-2; wherein each alkyl, aryl, heteroalkyl or heterocycle is optionally substituted with one or more of alkoxy, amino, cyano, halo, hydroxyl, or nitro.

In a particular example, the safe and efficacious amount is 300 mg/day or less (*e.g.*, 250, 200, 150, 100, or 50 mg/day or less). Particular patients are diabetic or pre-diabetic.

In one aspect, the present disclosure refers to a tablet comprising an API, croscarmellose sodium, silicon dioxide and microcrystalline cellulose, wherein the active pharmaceutical ingredient ("API") is crystalline anhydrous (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol.

In another aspect, the present disclosure refers to a granule comprising an API, croscarmellose sodium, collodial silicon dioxide, and microcrystalline cellulose, wherein the API is (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol.

4. BRIEF DESCRIPTION OF THE FIGURES

Certain aspects of this invention may be understood with reference to the figures. Figures 1-10 show results obtained from a randomized, double-blind, placebo controlled Phase 2a clinical trial, wherein 150 mg and 300 mg doses of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol were orally administered in solution once daily to patients with type 2 diabetes mellitus. Figure 11 provides results obtained from a Phase 1 clinical trial, wherein both solid and liquid oral dosage forms of the compound were administered to patients with type 2 diabetes mellitus.

FIG. 1 shows the plasma glucose levels of patients in the placebo group and in the 150 mg/day and 300 mg/day treatment groups over the course of the Phase 2a study.

FIG. 2 shows each group's mean results in a glucose tolerance test administered over the course of the study.

FIG. 3 shows each group's mean glucose plasma level area under the curve (AUC) over the course of the study.

FIG. 4 shows the results of each group's mean homeostatic model assessment (HOMA) value. Measurements were obtained before the study began and again on day 27.

FIG. 5 provides measurements of each group's mean post-prandial glucose level over the course of the study.

FIG. 6 provides measurements of each group's mean plasma fructosamine level over the course of the study.

FIG. 7 provides each group's mean percent change in hemoglobin A1c level over the course of the study.

FIG. 8 shows the change in each group's mean diastolic blood pressure as measured on day 28 of the study compared to baseline.

FIG. 9 shows the change in each group's mean systolic blood pressure as measured on day 28 of the study compared to baseline.

FIG. 10 shows the change in each group's mean arterial pressure as measured on day 28 of the study compared to baseline.

FIG. 11 shows the effects of a single dose of one of two solid formulations (6x50 mg tablets or 2x150 mg tablets) and a liquid formulation of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol on the total GLP-1 levels of patients with type 2 diabetes mellitus, as determined in a Phase 1 study.

CLAIMS

What is claimed is:

1. A tablet comprising an API, croscarmellose sodium, silicon dioxide and microcrystalline cellulose, wherein the active pharmaceutical ingredient ("API") is crystalline anhydrous (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol.

2. The tablet of claim 1, wherein the API is crystalline anhydrous (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol form 1 having a melting point of 123°C by DSC peak.

3. The tablet of claim 1, wherein the API is crystalline anhydrous (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol form 2 having a melting point of 134°C by DSC peak.

4. The tablet of claim 1, wherein the API is present in an amount of 300 mg or less.

5. The tablet of claim 1, which is coated.

6. The tablet of claim 1, which further comprises a second therapeutic agent, which second therapeutic agent is an anti-diabetic agent, anti-hyperglycemic agent, hypolipidemic/lipid lowering agent, anti-obesity agents, anti-hypertensive agent, or appetite suppressant.

7. The tablet of claim 6, wherein the second therapeutic agent is a dipeptidyl peptidase IV ("DPP-4") inhibitor.

8. The tablet of claim 7, wherein the DPP-4 inhibitor is sitagliptin or dutogliptin.

9. A granule comprising an API, croscarmellose sodium, collodial silicon dioxide, and microcrystalline cellulose, wherein the API is (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol.

10. The granule of claim 9, wherein the API is crystalline anhydrous (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol form 1 having a melting point of 123°C by DSC peak.

11. The granule of claim 9, wherein the API is crystalline anhydrous (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol form 2 having a melting point of 134°C by DSC peak.