retention effect generally associated with ERAs, to the beneficial pharmacological effects mentioned above, and potentially to additional beneficial pharmacological effects associated with blood viscosity. Finally, aprocitentan which has the pharmacological effect of a dual ERA may be particularly suited for such combination therapy when compared to a selective ET_A receptor antagonist, as it may have low counteracting activity on the beneficial effect of SGLT-2 inhibitors on sodium re-uptake that is associated to the principal pharmacological effect of SGLT-2 on glucose re-uptake.

It has further been found that certain crystalline forms of aprocitentan that are suitable for the production of pharmaceutical compositions may under certain conditions be found. Said crystalline forms of aprocitentan may have advantageous properties in view of the potential use of aprocitentan as active pharmaceutical ingredient. Such advantages may include better flow properties; less hygroscopicity; better reproducibiliy in manufacturing (for example better filtration parameters, better reproducibility of formation, and/or better sedimentation); and/or defined morphology. Such crystalline forms of aprocitentan may be particularly suitable in a process of manufacturing certain pharmaceutical compositions. It has also been found that aprocitentan or a pharmaceutically acceptable salt thereof is particularly useful to treat certain disorders, in particular when used in combination with other active ingredients or therapeutic agents.

Summary

In one aspect, the present disclosure provides a pharmaceutical composition containing, as active principles, aprocitentan, or a pharmaceutically acceptable salt thereof, in combination with an SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof, as well as at least one pharmaceutically acceptable excipient.

In another aspect, there is provided a use of aprocitentan, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for preventing or treating chronic kidney disease (CKD), including CKD caused by / associated with hypertension, and/or caused by / associated with diabetes; acute or chronic renal failure; diabetic nephropathy; or glomerulonephritis; for preventing or treating diabetes, and diabetes related diseases including diabetic arteriopathy, diabetic retinopathy, or diabetic vasculopathy; diabetic complications; for reducing the risk of developing a major cardiovascular event in patients who have diabetes, including patients who have diabetes that is accompanied by at least one other cardiovascular risk factor; or for preventing or treating diabetic foot ulcers and/or for reducing the risk of lower extremety amputations in patients who have diabetes; for preventing or treating heart failure including systolic heart failure and diastolic heart failure; for reducing the risk of developing a major cardiovascular event in patients who are at cardiovascular risk; or for preventing or treating ischemic heart diseases including angina pectoris, coronary diseases, and myocardial ischemia; cardiac insufficiency; or diastolic dysfunction; for treating hypertension including resistant hypertension; for preventing or treating atherosclerosis; or peripheral arterial obliterant disease including chronic peripheral arteriopathy; for preventing or treating digital ulcers; or preventing or treating connective tissue diseases; wherein aprocitentan is to be administered in combination with an SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof.

Description of the Figures

Figure 1 shows the X-ray powder diffraction diagram of COMPOUND in a crystalline form A as obtained from Example 1. The X-ray diffraction diagram shows peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensitites given in parenthesis) at the indicated angles of refraction 2theta (selected peaks from the range 3-33° 2theta with relative intensity larger then 10% are reported): 9.8° (18%), 9.9° (18%), 11.7° (14%), 14.5° (10%), 15.4° (14%), 15.6° (29%), 16.9° (19%), 17.2° (16%), 17.8° (100%), 18.6° (50%), 19.9° (54%), 20.0° (67%), 21.5° (24%), 21.9° (10%), 22.8° (18%), 23.2° (49%), 23.5° (83%), 24.9° (32%), 25.1° (20%), 25.3° (24%), 25.6° (33%), 25.9° (16%), 27.1° (23%), 27.3° (39%), 28.5° (13%), 29.0° (23%), 29.4° (15%), 30.1° (12%) and 30.6° (10%).

Figure 2 shows the X-ray powder diffraction diagram of COMPOUND in a crystalline form C as obtained from Example 2. The X-ray diffraction diagram shows peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensitites given in parenthesis) at the indicated angles of refraction 2theta (selected peaks from the range 3-33° 2theta with relative intensity larger then 10% are reported): 7.8° (23%), 9.7° (42%), 15.7° (37%), 17.2° (16%), 17.8° (15%), 18.8° (26%), 19.8° (71%), 20.1° (51%), 20.6° (15%), 21.6° (15%), 22.0° (100%), 23.4° (27%), 23.6° (40%), 24.1° (23%), 24.5° (16%), 25.1° (13%), 25.3° (39%), 25.7° (28%), 26.8° (19%), 27.1° (16%), 28.5° (31%), 30.8° (13%) and 30.8° (13%).

It is understood, that the crystalline forms disclosed herein comprise the COMPOUND in a crystalline form of the free base (i.e. not in form of a salt). Furthermore, said crystalline forms may comprise non-coordinated and

Claims

1. A pharmaceutical composition containing, as active principles, aprocitentan, or a pharmaceutically acceptable salt thereof, in combination with an SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof, as well as at least one pharmaceutically acceptable excipient.

2. The pharmaceutical composition according to claim 1, wherein the SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof, is atigliflozin, bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, henagliflozin, ipragliflozin, luseogliflozin, remogliflozin, sotagliflozin, or tofogliflozin, or a pharmaceutically acceptable salt thereof.

3. The pharmaceutical composition according to claim 1, wherein the SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof, is canagliflozin, or a pharmaceutically acceptable salt thereof.

4. The pharmaceutical composition according to any one of claims 1 to 3 wherein aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 10 to 50 mg per day of aprocitentan.

5. The pharmaceutical composition according to claim 3, wherein

- aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 10 to 50 mg per day of aprocitentan; and
- canagliflozin, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 50 to 400 mg per day of canagliflozin.

6. The pharmaceutical composition according to any one of claims 1 to 5, said composition comprising aprocitentan in crystalline form, wherein said crystalline form is characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 17.8°, 18.6°, 20.0°, 23.2° and 23.5°; wherein said X-ray powder diffraction diagram is obtained by using combined Cu Kα1 and Kα2 radiation, without Kα2 stripping; and the accuracy of the 2θ values is in the range of 2θ +/- 0.2°.

7. Use of aprocitentan, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament

- for preventing or treating chronic kidney disease (CKD), including CKD caused by / associated with hypertension, and/or caused by / associated with diabetes; acute or chronic renal failure; diabetic nephropathy; or glomerulonephritis;
- for preventing or treating diabetes, and diabetes related diseases including diabetic arteriopathy, diabetic retinopathy, or diabetic vasculopathy; diabetic complications; for reducing the risk of developing a major cardiovascular event in patients who have diabetes, including patients who have diabetes that is accompanied by at least one other cardiovascular risk factor; or for preventing or

treating diabetic foot ulcers and/or for reducing the risk of lower extremety amputations in patients who have diabetes;

- for preventing or treating heart failure including systolic heart failure and diastolic heart failure; for reducing the risk of developing a major cardiovascular event in patients who are at cardiovascular risk; or for preventing or treating ischemic heart diseases including angina pectoris, coronary diseases, and myocardial ischemia; cardiac insufficiency; or diastolic dysfunction;
- for treating hypertension including resistant hypertension;
- for preventing or treating atherosclerosis; or peripheral arterial obliterant disease including chronic peripheral arteriopathy;
- for preventing or treating digital ulcers; or
- for preventing or treating connective tissue diseases;

wherein aprocitentan is to be administered in combination with an SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof.

8. The use according to claim 7

- for preventing or treating CKD caused by / associated with hypertension;
- for preventing or treating diabetic kidney disease (DKD);
- for preventing or treating chronic renal failure caused by / associated with hypertension or caused by / associated with diabetes; diabetic nephropathy; or glomerulonephritis caused by / associated with hypertension;
- for reducing the risk of developing a major cardiovascular event in patients who have diabetes, including in patients who have diabetes that is accompanied by at least one other cardiovascular risk factor;
- for preventing or treating diabetic foot ulcers and/or for reducing the risk of lower extremety amputations in patients who have diabetes; or
- for preventing or treating heart failure including systolic heart failure and diastolic heart failure;

wherein aprocitentan is to be administered in combination with an SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof.

9. The use according to claim 7 for treating diabetic kidney disease (DKD) associated, in addition, with hypertension.

10. The use according to any one of claims 7, 8 or 9; wherein said SGLT-2 inhibitor is atigliflozin, bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, henagliflozin, ipragliflozin, luseogliflozin, remogliflozin, sotagliflozin, or tofogliflozin, or a pharmaceutically acceptable salt thereof.

11. The use according to any one of claims 7, 8 or 9; wherein said the SGLT-2 inhibitor is canagliflozin, dapagliflozin, or empagliflozin, or a pharmaceutically acceptable salt thereof.

12. The use according to any one of claims 7, 8 or 9; wherein said the SGLT-2 inhibitor is canagliflozin, or a pharmaceutically acceptable salt thereof.

13. The use according to any one of claims 7 to 12; wherein aprocitentan, or a pharmaceutically acceptable salt thereof, is to be administered in a pharmaceutical unit dosage form suitable for the oral administration of 10 to 50 mg per day of aprocitentan.

14. The use according to claim 11; wherein aprocitentan, or a pharmaceutically acceptable salt thereof, is to be administered in a pharmaceutical unit dosage form suitable for the oral administration of 10 to 50 mg per day of aprocitentan; and

- canagliflozin, or a pharmaceutically acceptable salt thereof, if present, is to be administered in a pharmaceutical unit dosage form suitable for the oral administration of 50 to 400 mg per day of canagliflozin;
- dapagliflozin, or a pharmaceutically acceptable salt thereof, if present, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 1 to 20 mg per day of dapagliflozin; and
- empagliflozin, or a pharmaceutically acceptable salt thereof, if present, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 5 to 50 mg per day of empagliflozin.