Claims

1. A pharmaceutical composition containing, as active principles, aprocitentan, or a pharmaceutically acceptable salt thereof, in combination with an SGLT-2 inhibitor, which is bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, remogliflozin, or tofogliflozin; or a pharmaceutically acceptable salt thereof, as well as at least one pharmaceutically acceptable excipient;
wherein said pharmaceutical composition is

- 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 reducing the risk of developing a major cardiovascular event in patients who have diabetes, wherein said diabetes is accompanied by at least one other cardiovascular risk factor comprising hypertension; or
- for treating hypertension including resistant hypertension.

2. The pharmaceutical composition according to claim 1, wherein said composition is

- for preventing or treating CKD caused by / associated with hypertension;
- for preventing or treating diabetic kidney disease (DKD)) associated, in addition, with hypertension;
- 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; or
- for reducing the risk of developing a major cardiovascular event in patients who have diabetes, wherein said diabetes is accompanied by at least one other cardiovascular risk factor comprising hypertension.

~~2~~3. The pharmaceutical composition according to claim 1 or 2, wherein the SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof, is ~~atigliflozin, bexagliflozin,~~ canagliflozin, dapagliflozin, or 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~~ or 2, 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, if present, is comprised 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.

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~~ wherein said diabetes ~~that~~ is accompanied by at least one other cardiovascular risk factor comprising hypertension~~; 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 which is bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, remogliflozin, or tofogliflozin;~~,~~ or a pharmaceutically acceptable salt thereof.

8. The use according to claim 7, wherein said medicament is

- for preventing or treating CKD caused by / associated with hypertension;
- for preventing or treating diabetic kidney disease (DKD) associated, in addition, with hypertension;
- 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; or
- ~~for reducing the risk of developing a major cardiovascular event in patients who have diabetes, including in patients who have~~ wherein said diabetes ~~that~~ is accompanied by at least one other cardiovascular risk factor comprising hypertension~~;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 wherein said medicament is 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, or 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~~**11.** The use according to any one of claims 7, 8 or 9 ~~to 12~~; wherein said medicament comprises 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~~**12.** The use according to claim ~~11~~10; wherein said medicament comprises 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 wherein

- 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 to be administered ~~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~~ to be administered in a pharmaceutical unit dosage form suitable for the oral administration of 5 to 50 mg per day of empagliflozin.

13. The use according to any one of claims 7, 8 or 9, wherein said medicament is further to be administered in combination / as co-therapy to conventional background therapy suitable for the prevention or treatment of hypertension; chronic kidney disease (CKD); or diabetes.

14. The use according to claim 13, wherein said conventional background therapy comprises

- an angiotensin converting enzyme (ACE) inhibitor, or a pharmaceutically acceptable salt thereof; and/or
- an angiotensin receptor blocker (ARB), or a pharmaceutically acceptable salt thereof; and/or
- a calcium channel blocker, or a pharmaceutically acceptable salt thereof;
- and/or metformin; and/or
- insulin; and/or
- a sulfonylurea, or a pharmaceutically acceptable salt thereof; and/or
- a DPP-4 inhibitor, or a pharmaceutically acceptable salt thereof; and/or
- a GLP-1 receptor agonist; and/or
- a thiazolidinedione, or a pharmaceutically acceptable salt thereof.