Claims

1. Use of aprocitentan, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of difficult to control or resistant hypertension in a human subject, wherein said medicament comprises a clinically proven effective amount of aprocitentan, or a pharmaceutically acceptable salt thereof.

2. The use according to claim 1, wherein said human subject, before treatment with said medicament, receives standard background therapy wherein said background therapy comprises first line therapies suitable for the prevention or treatment of hypertension, said background therapy comprising especially an angiotenin receptor blocker (ARB) or an ACE inhibitor, notably further in combination with a calcium channel blocker (CCB) and/or a diuretic; and optionally further in combination with a beta blocker.

3. The use according to claim 1 or 2, wherein said medicament is to be administered in combination with at least three other antihypertensive drugs independently selected from the group consisting of

- an angiotenin receptor blocker, or a pharmaceutically acceptable salt thereof; or
  an ACE inhibitor, or a pharmaceutically acceptable salt thereof;
- a calcium channel blocker, or a pharmaceutically acceptable salt thereof;
- a diuretic; and
- a beta blocker (beta-adrenergic blocking agent).

4. The use according to any one of claims 1 to 3, wherein the administration of said medicament comprising said clinically proven effective amount of aprocitentan results in a reduction of systolic blood pressure of at least about 12 mmHg from baseline after 4 weeks of treatment, wherein said reduction is measured by unattended Automated Office Blood Pressure Measurement (uAOBPM) at trough.

5. The use according to any one of claims 1 to 4, wherein the administration of said medicament comprising said clinically proven effective amount of aprocitentan for an additional 32 weeks after said initial 4 weeks of treatment results at least in the maintenance of the mean reduction from baseline in systolic blood pressure for such additional 32 weeks.

6. The use according to claim 4, wherein the clinical effect on systolic blood pressure is confirmed after 4 weeks of a withdrawal period, wherein the mean systolic blood pressure increases in subjects administered with placebo compared to the mean systolic blood pressure in subjects who continue to be administered with aprocitentan at a dose of 25 mg per day; wherein said increase is at least about 6 mmHg; wherein said increase is measured by unattended Automated Office Blood Pressure Measurement (uAOBPM) at trough.

7. The use according to any one of claims 4 to 6, wherein said clinical effect on blood pressure reduction is confirmed by a mean reduction from baseline blood pressure after 4 weeks of treatment, wherein said reduction is measured by 24 hours ambulatory blood pressure monitoring (24h ABPM); wherein

- systolic blood pressure is reduced by at least about 6 mmHg, and/or
  diastolic blood pressure is reduced by at least about 6 mmHg,

wherein said clinically proven effective amount of aprocitentan is 12.5 mg per day; or

- systolic blood pressure is reduced by at least about 8 mmHg, and/or
  diastolic blood pressure is reduced by at least about 7 mmHg,
  wherein said clinically proven effective amount of aprocitentan is 25 mg per day.

8. The use according to any one of claims 4 to 6, wherein said clinical effect on blood pressure reduction is confirmed by a mean reduction from baseline blood pressure after 4 weeks of treatment, wherein said reduction is measured by nighttime ambulatory blood pressure monitoring (nighttime ABPM); wherein

- systolic blood pressure is reduced by at least about 6 mmHg, and/or
  diastolic blood pressure is reduced by at least about 6 mmHg,
  wherein said clinically proven effective amount of aprocitentan is 12.5 mg per day; or
- systolic blood pressure is reduced by at least about 8 mmHg, and/or
  diastolic blood pressure is reduced by at least about 7 mmHg,
  wherein said clinically proven effective amount of aprocitentan is 25 mg per day.

9. The use according to any one of claims 1 to 8, wherein the administration of said medicament comprising said clinically proven effective amount of aprocitentan results in a mean placebo corrected reduction of blood pressure after 4 weeks of treatment, wherein said reduction is measured by 24 hours ambulatory blood pressure monitoring (24h ABPM); wherein

- systolic blood pressure is reduced by at least about 4 mmHg, and/or
  diastolic blood pressure is reduced by at least about 5.5 mmHg,
  wherein said clinically proven effective amount of aprocitentan is 12.5 mg per day; or
- systolic blood pressure is reduced by at least about 4 mmHg, and/or
  diastolic blood pressure is reduced by at least about 5.5 mmHg,
  wherein said clinically proven effective amount of aprocitentan is 25 mg per day.

10. The use according to any one of claims 1 to 8, wherein the administration of said medicament comprising said clinically proven effective amount of aprocitentan results in a mean placebo corrected reduction of blood pressure after 4 weeks of treatment, wherein said reduction is measured by nighttime ambulatory blood pressure monitoring (nighttime ABPM); wherein

- systolic blood pressure is reduced by at least about 4 mmHg, and/or
  diastolic blood pressure is reduced by at least about 4 mmHg,
  wherein said clinically proven effective amount of aprocitentan is 12.5 mg per day;
  wherein, especially, said medicament is to be administered once a day in the morning; or
- systolic blood pressure is reduced by at least about 4 mmHg, and/or
  diastolic blood pressure is reduced by at least about 5.5 mmHg,
  wherein said clinically proven effective amount of aprocitentan is 25 mg per day;
  wherein, especially, said medicament is to be administered once a day in the morning.

11. The use according to any one of claims 4 to 6, wherein the reduction of blood pressure is confirmed after 4 weeks of a withdrawal period, wherein the mean blood pressure increases in subjects administered with placebo compared to the respective mean blood pressure in subjects who continue to be administered with aprocitentan at a dose of 25 mg per day; wherein said mean blood pressure increase in subjects administered with placebo is measured by nighttime ambulatory blood pressure monitoring (nighttime ABPM); wherein

- systolic blood pressure is increased by at least about 8.5 mmHg, and/or
  diastolic blood pressure is increased by at least about 7.5 mmHg;

wherein, especially, said medicament is to be administered once a day in the morning.

12. The use according to any one of claims 1 to 11, wherein said medicament comprises a pharmaceutical composition comprising a clinically proven safe and clinically proven effective amount of aprocitentan.

13. The use according to any one of claims 1 to 12, wherein the clinically proven effective amount, respectively, the clinically proven safe and clinically proven effective amount of aprocitentan is 12.5 mg or 25 mg per day of aprocitentan wherein if aprocitentan is to be administered in pharmaceutically acceptable salt form, the amount refers to the free base equivalent.

14. The use according to any one of claims 1 to 12, wherein the clinically proven effective amount, respectively, the clinically proven safe and clinically proven effective amount of aprocitentan is 12.5 mg per day of aprocitentan wherein if aprocitentan is to be administered in pharmaceutically acceptable salt form, the amount refers to the free base equivalent.

15. The use according to any one of claims 1 to 12, wherein the clinically proven effective amount, respectively, the clinically proven safe and clinically proven effective amount of aprocitentan is 25 mg per day of aprocitentan wherein if aprocitentan is to be administered in pharmaceutically acceptable salt form, the amount refers to the free base equivalent.

16. The use according to any one of claims 1 to 15; wherein said human subject, before treatment with said medicament, has chronic kidney disease (CKD) of stage 3 or 4.

17. The use according to any one of claims 1 to 15; wherein said human subject, before treatment with said medicament, has at least one of a urine albumin-to-creatinine ratio (UACR) of > 300 mg/g and an estimated glomerular filtration rate (eGFR) of 15 to < 60 mL/min per 1.73 m2.

18. The use according to any one of claims 1 to 15; wherein said human subject, before treatment with said medicament, is obese.

19. The use according to any one of claims 1 to 18; wherein said human subject, before treatment with said therapeutic agent, has a systolic blood pressure ≥ 140 mmHg despite treatment with at least three antihypertensive medications.