pulmonary artery pressure (PAP) > 20 mm Hg, a pulmonary artery wedge pressure (PAWP) ≤ 15 mm Hg and a PVR of ≥ 3 Wood units, alternatively > 2 Wood units, all measured at rest. There are unresolved chronic blood clots in the lungs that lead to pulmonary artery occlusions and / or stenosis.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a complication of pulmonary embolism and a major cause of chronic PH leading to right heart failure and death [Kim et al., Chronic thromboembolic pulmonary hypertension. *Eur. Respir. J.* (2018), in press (https://doi.org/10.1183/13993003.01915-2018)]. Lung ventilation/perfusion scintigraphy is the screening test of choice; a normal scan rules out CTEPH. In the case of an abnormal perfusion scan, a high-quality pulmonary angiogram is necessary to confirm and define the pulmonary vascular involvement and prior to making a treatment decision. PH is confirmed with right heart catheterisation, which is also necessary for treatment determination. In addition to chronic anticoagulation therapy, each patient with CTEPH should receive treatment assessment starting with evaluation for pulmonary endarterectomy, which is the guideline recommended treatment. For technically inoperable cases, PH-targeted medical therapy is recommended (currently riociguat based on the CHEST studies), and balloon pulmonary angioplasty should be considered at a centre experienced with this challenging but potentially effective and complementary intervention.

SUMMARY ~~OF THE INVENTION~~

It is an object of the present ~~invention~~ disclosure to provide a medication and/or treatment regimen for chronic thromboembolic pulmonary hypertension (CTEPH). It is a further object of the present invention to provide a combination medication and/or treatment for CTEPH. Moreover, it is an object of the present invention to provide the medication and/or treatment regimen or combination medication to specific patient populations with CTEPH. Moreover, it is an object of the present invention to provide a pharmaceutical composition for use in the treatment of CTEPH.

In an aspect, there is provided the use of macitentan in the manufacture of a medicament for the treatment and/or prevention of chronic thromboembolic pulmonary hypertension (CTEPH) in human, wherein the dosage of macitentan is from 60 to 90 mg per day.

In another aspect, there is provided the use of a pharmaceutical composition in the manufacture of a medicament for the treatment of CTEPH, the pharmaceutical

composition comprising macitentan and at least a pharmaceutically acceptable excipient, containing macitentan in an amount of 25 to 50 mg or 60 to 90 mg.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a dose-response curve showing the change in hemoglobin (HGB) in function of the dose of macitentan administered to a human.

DETAILED DESCRIPTION

The present inventors have recognized that, despite fears of clinically relevant hemoglobin decreases, blood pressure decreases and/or edema or fluid retention increases, it is

Claims

1) Use of m~~M~~acitentan ~~for use~~ in the manufacture of a medicament for the treatment and/or prevention of chronic thromboembolic pulmonary hypertension (CTEPH) in human, wherein the dosage of macitentan is from 60 to 90 mg per day.

2) ~~Macitentan for~~The use ~~in the treatment and/or prevention of chronic thromboembolic pulmonary hypertension (CTEPH)~~ according to claim 1, wherein the dosage of macitentan is from 70 to 80 mg per day.

3) ~~Macitentan for~~The use ~~in the treatment and/or prevention of CTEPH~~ according to claim 1 or 2, wherein the dosage of macitentan is 75 mg per day.

4) ~~Macitentan for~~The use ~~in the treatment and/or prevention of CTEPH~~ according to any one of claims 1 to 3, wherein the dosages are given once per day.

5) ~~Macitentan for~~The use ~~in the treatment and/or prevention of CTEPH~~ according to any one of claims 1 to 3, wherein the dosage of macitentan is 35 to 40 mg twice per day.

6) ~~Macitentan for~~The use ~~in the treatment and/or prevention of CTEPH~~ according to claim 5, wherein the dosage of macitentan is 37.5 mg twice per day.

7) ~~Macitentan for~~The use ~~in the treatment and/or prevention of CTEPH~~ according to claim 1, wherein the dosage of macitentan is escalated from 10 mg per day, followed by 25 to 50 mg per day, and followed by 60 to 90 mg per day.

8) The ~~Macitentan for~~ use ~~in the treatment and/or prevention of CTEPH~~ according to claim 7, wherein the dosage of macitentan is escalated from 10 mg per day, followed by 37.5 mg per day, and followed by 75 mg per day.

9) ~~Macitentan for~~The use ~~in the treatment and/or prevention of CTEPH~~ according to claim 1 or 2, wherein the dosage of macitentan is escalated from 10 mg per day, followed by 37.5 mg per day, followed by 75 mg per day.

10) ~~Macitentan for~~The use ~~in the treatment and/or prevention of CTEPH~~ according to claim 9, wherein the dosage of macitentan is escalated from 10 mg per day, followed by 75 mg once per day or 37.5 mg twice a day.

11) The ~~Macitentan for~~ use ~~in the treatment and/or prevention of CTEPH~~ according to any one of claims 7 to 10, wherein the lower dosage of macitentan is applied for 15 to 45 days in case it is followed by a higher dose.

12) ~~Macitentan for~~The use ~~in the treatment and/or prevention of CTEPH~~ according to claim 7, wherein the dosage of macitentan is escalated from 10 mg once per day, for 15 to 45 days; followed by 25 to 50 mg per day, for 15 to 45 days; and followed by 60 to 90 mg per day.

13) ~~Macitentan for~~ The use ~~in the treatment and/or prevention of CTEPH~~ according to claim 12, wherein the dosage of macitentan is escalated from 10 mg once per day for 15 to 45 days; followed by 37.5 mg once per day for 15 to 45 days; and followed by 75 mg once per day or 37.5 mg twice per day.

14) ~~Macitentan for~~The use ~~in the treatment and/or prevention of CTEPH~~ according to any one of claims 1 to 3, provided that the patient is already treated with an endothelin receptor antagonist preferably selected from bosentan and ambrisentan.

15) ~~Macitentan for~~The use ~~in the treatment and/or prevention of CTEPH~~ according to any one of claims 1 to 14, wherein macitentan is combined with a PDE5 inhibitor and/or a prostacyclin analogue, and/or a prostacyclin receptor agonist and/or a soluble guanylate cyclase stimulator.

16) ~~Macitentan for t~~The use ~~in the treatment and/or prevention of CTEPH~~ according to claim 15, wherein the PDE5 inhibitor is selected from sildenafil, tadalafil, vardenafil, and udenafil; the prostacyclin analogue is selected from epoprostenol, treprostinil, iloprost, and beraprost; the prostacyclin receptor agonist is selected from selexipag and ralinepag; and the soluble guanylate cyclase stimulator is selected from riociguat, olinciguat, praliciguat and vericiguat.

17) ~~Macitentan for t~~The use ~~in the treatment and/or prevention of CTEPH~~ according to claim 15 or 16, wherein macitentan is combined with tadalafil and/or selexipag and/or riociguat, preferably with riociguat.

18) ~~Macitentan for t~~The use ~~in the treatment and/or prevention of CTEPH~~ according to claim 17, wherein macitentan is combined with riociguat and riociguat has a dosage of 0.5 mg three times per day to 2.5 mg three times per day, preferably 2.5 mg three times per day.

19) ~~Macitentan for t~~The use ~~in the treatment and/or prevention of CTEPH~~ according to any one of claims 1 to 18, wherein macitentan is for patients before PEA surgery.

20) ~~Macitentan for t~~The use ~~in the treatment and/or prevention of CTEPH~~ according to any one of claims 1 to 18, wherein the patient to be treated is inoperable with PEA surgery.

21) ~~Macitentan for t~~The use ~~in the treatment and/or prevention of CTEPH~~ according to any one of claims 1 to 18, wherein the patient to be treated suffers from persistent or recurrent PH after PEA surgery.

22) ~~Macitentan for t~~The use ~~in the treatment and/or prevention of CTEPH~~ according to any one of claims 1 to 18, wherein the patient to be treated has been treated with BPA and PEA surgery.

23) ~~Macitentan for t~~The use ~~in the treatment and/or prevention of CTEPH~~ according to any one of claims 1 to 18, wherein the patient to be treated is excluded from BPA.

24) ~~Macitentan for t~~The use ~~in the treatment and/or prevention of CTEPH~~ according to any one of claims 1 to 18, wherein the patient to be treated suffers from persistent or recurrent PH after BPA.

25) ~~Macitentan for~~The use ~~in the treatment and/or prevention of CTEPH~~ according to any one of claims 1 to 24, wherein the treatment and/or prevention means the reduction of morbidity and/or mortality risk of CTEPH.

26) Use of ~~A~~a pharmaceutical composition ~~for use~~ in the manufacture of a medicament for the treatment of CTEPH, the pharmaceutical composition comprising macitentan and at least a pharmaceutically acceptable excipient, containing macitentan in an amount of 25 to 50 mg or 60 to 90 mg.

27) ~~A pharmaceutical composition~~The use according to claim 26, ~~which~~ wherein the pharmaceutical composition contains macitentan in an amount of 37.5 mg or 75 mg.

28) The ~~pharmaceutical composition~~use according to claim 26 or 27, ~~which~~ wherein the pharmaceutical composition comprises

(i) macitentan in a total amount of 10 to 50% in weight based on the total weight of the pharmaceutical composition,

(ii) a filler, consisting of lactose monohydrate with microcrystalline cellulose, in a total amount of 10 to 85% in weight based on the total weight of the pharmaceutical composition,

(iii) a disintegrant, consisting of sodium starch glycolate or a combination of sodium starch glycolate and polyvinylpyrrolidone, in a total amount of 1 to 10% in weight based on the total weight of the pharmaceutical composition,

(iv) a surfactant, consisting of a polysorbate, in a total amount of 0.1 to 1% in weight based on the total weight of the pharmaceutical composition, and

(v) a lubricant, consisting of magnesium stearate, in a total amount of 0.05 to 5% in weight based on the total weight of the pharmaceutical composition.

29) The ~~pharmaceutical composition~~use according to claim 26 or 28, ~~which~~ wherein the pharmaceutical composition is in the form of a capsule or a tablet.