In particular, the present invention focuses on PAH which is haemodynamically characterised by the presence of a mean pulmonary artery pressure (PAP) ≥ 25 mm Hg, a pulmonary artery wedge pressure (PAWP) ≤ 15 mm Hg and a PVR of equal to or more than (>) 3 Wood units, alternatively > 2 Wood units, all measured at rest.

The pathophysiology of PAH is characterised by an imbalance between molecules mediating vasoconstriction (e.g., endothelin or thromboxane) and/or molecules mediating vasodilation (e.g., prostacyclin and nitric oxide). Furthermore, mitogenic effects of these molecules, with specific pathomorphological changes in the pulmonary circulation are involved in disease progression.

Currently available compounds approved for specific treatment of PAH are in three different groups: a) endothelin receptor antagonists, b) phosphodiesterase type 5 inhibitors (PDE5is) and soluble guanylate cyclase stimulators, and c) molecules interfering with the prostacyclin pathway. Treatment with these compounds in combination with general measures has increased 3-year survival after first diagnosis of idiopathic PAH from 48% in the 1980s to 74% in the last two decades, as shown in the REVEAL registry (Benza et al., An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. *CHEST* (2012), **142**(2), 448–456; and *CHEST* (2012), **141**(2):354–362).

SUMMARY

It is an object of the present disclosure to provide a medication and/or treatment regimen for pulmonary arterial hypertension (PAH). In particular it is an object of the present invention to provide a medication and/or treatment regimen for the treatment of mild or moderate PAH. It is a further object of the present invention to provide a combination medication and/or treatment for PAH.

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

In another aspect, there is provided the se of a pharmaceutical composition in the manufacture of a medicament for the treatment of PAH, 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 possible and safe and effective to treat PAH patients with high doses of macitentan. In particular, it is possible to decrease the progress of the disease, or even to improve the status of the disease.

Claims

1) Use of macitentan in the manufacture of a medicament for the treatment and/or prevention of pulmonary arterial hypertension (PAH) in human, wherein the dosage of macitentan is 60 to 90 mg per day.

2) The use according to claim 1, wherein the dosage of macitentan is 70 to 80 mg per day.

3) The use according to claim 1 or 2, wherein the dosage of macitentan is 75 mg per day.

4) The use according to one of claims 1 to 3, wherein the PAH is mild or moderate PAH.

5) The use according to any one of claims 1 to 4, wherein the dosage of macitentan is 30 to 45 mg twice per day.

6) The use according to claim 5, wherein the dosage of macitentan is 37.5 mg twice per day.

7) The use according to claim 4, 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 use 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) The use according to any one of claims 1 to 4, wherein the dosage of macitentan is escalated from 10 mg per day, followed by 60 to 90 mg per day.

10) The use 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 use 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.

12) The use according to claim 11, 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.

13) The use according to any one of claims 1 to 4, provided that the patient is already treated with an endothelin receptor antagonist preferably selected from bosentan and ambrisentan.

14) The use according to any one of claims 1 to 13, 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.

15) The use according to claim 14, 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 and vericiguat.

16) The use according to claim 14 or 15, wherein macitentan is combined with tadalafil and/or selexipag or ralinepag, preferably with tadalafil and/or selexipag.

17) The use according to claim 16, wherein tadalafil, if applicable, has a dose of 20 to 40 mg per day, preferably 40 mg per day, selexipag, if applicable, has a dose of 0.2 to 1.6 mg twice per day and ralinepag, if applicable, has a dose of 0.05 to 1.45 mg per day.

18) The use according to any one of claims 1 to 17, wherein the treatment and/or prevention means the reduction of morbidity and/or mortality risk of PAH.

19) Use of a pharmaceutical composition in the manufacture of a medicament for the treatment of PAH, 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.

20) The use according to claim 19, wherein the pharmaceutical composition contains macitentan in amount of 37.5 mg or 75 mg.

21) The use according to claim 19 or 20, 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.

22) The use according to any one of claims 19 to 21, wherein the pharmaceutical composition is in the form of a capsule or a tablet.