readily tolerated in normal physiology may result in progressive failure of the Fontan circulation. Importantly, high PVR is a strong predictor of mortality (Griffiths et al., *Ann. Thorac. Surg.* (2009), **88**, 558-563).

[0007] Prostacyclins have been rarely used in perioperative Fontan patients; beraprost reduces mean pulmonary artery pressure (PAP) and PVR in preoperative Fontan candidates with mild pulmonary hypertension, (Takahashi et al., *Pediatr. Int.* (2003), **45**, 671-675) and epoprostenol has been shown to prevent the rebound effect after inhaled nitric oxide (NO) cessation in the early postoperative phase (Miyaji et al., *J. Thorac. Cardiovasc. Surg.* (2003), **125**, 437-439). When oral administration becomes possible, sildenafil is often used in the postoperative period as it is perceived as safe, with fast onset and good effectiveness. However, none of these medications (beraprost, epoprostenol, or sildenafil) are approved for these uses and there are no published data to confirm their efficacy or safety in this indication.

[0008] Bosentan has been shown to improve exercise capacity, functional class, health-related quality of life and haemodynamic parameters (including PVR and PAP) in patients with pulmonary arterial hypertension (PAH) (Gabbay et al., *Vasc. Health Risk Manag.* (2007), **3**, 887-900; Valerio and Coghlan, *Vasc. Health Risk Manag.* (2009), **5**, 607-619). Long-term treatment with bosentan improved symptoms and aortic oxygen saturation, functional class, maximal and submaximal exercise capacity, the Borg dyspnoea index, mean PAP, pulmonary blood flow and PVR in a patient with plastic bronchitis following Fontan (Apostolopoulou et al., *J. Heart Lung Transplant.* (2005), **24**, 1174-1176; and Hebert et al., "The effect of Bosentan on exercise capacity in Fontan patients; rationale and design for the TEMPO study," *BMC Cardiovasc. Disord.* 2013; 13: 36). The effect of long-term bosentan treatment on the liver is a potential concern for treating Fontan patients, especially in patients with hepatic complications. However, bosentan is not approved for these uses.

[0009] Given the important role of the pulmonary vascular circulation in Fontan physiology and the demonstrated increase in PAP with age, there is a major requirement for the development of effective and safe medical prevention or treatment for patients with worsening or failed Fontan system.

SUMMARY OF THE ~~INVENTION~~DISCLOSURES

[0010] It is an object of the present ~~invention~~ disclosure to provide a medication and/or treatment regimen for pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated

patients. In particular it is an object of the present ~~invention~~ disclosure to improve the oxygen

uptake / consumption (peak VO_2) by the body. It is a further object of the present ~~invention~~ disclosure to reduce morbidity and/or mortality risk of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients. It is a further object of the present ~~invention~~ disclosure to provide a combination medication and/or treatment for pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients.

[0010a] In an aspect, there is provided the use of macitentan in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients, wherein the dosage of macitentan is from 20 mg per day to 300 mg per day.

[0010b] In another aspect, there is provided the use of a pharmaceutical composition comprising macitentan in an amount of 20 mg to 300 mg and at least a pharmaceutically acceptable excipient, in the manufacture of a medicament in the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients.

[0010c] in yet another aspect, there is provided the use of aprocitentan in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients, wherein the dosage of aprocitentan is 100 mg per day to 1500 mg per day.

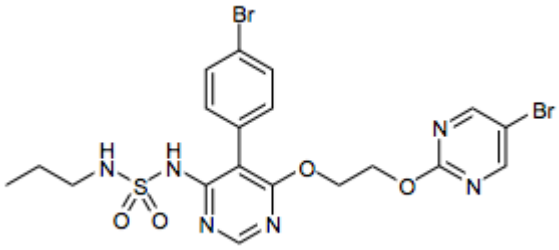
BRIEF DESCRIPTION OF THE FIGURES

[0011] 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

[0012] The present inventors have recognized that, despite the potential occurrence of clinically relevant hemoglobin decreases, blood pressure decreases and/or edema or fluid retention increases, it is possible and safe and effective to treat pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients with high doses of macitentan. In particular, it is possible to decrease the progress of pulmonary vascular disease and/or cardiac dysfunction, or even to improve the status of the pulmonary vascular disease and/or cardiac dysfunction.

[0013] In the present invention, macitentan is defined as propylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide, i.e. a compound of formula (I)



(I)

[0014] or a pharmaceutically acceptable salt, solvate, hydrate or morphological form thereof.

[0015] Macitentan is an endothelin receptor antagonist (ERA) that acts as an antagonist of two endothelin (ET) receptor subtypes, ET_A and ET_B (Kholdani et al, Macitentan for the treatment of pulmonary arterial hypertension. *Vasc. Health Risk Manag.* (2014), **10**, 665-673).

Claims

1. Use of ~~M~~macitentan ~~for use~~ in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients, wherein the dosage of macitentan is from 20 mg per day to 300 mg per day.

2. The use of ~~M~~macitentan ~~for use~~ in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to claim 1, wherein the treatment means the reduction of morbidity and/or mortality risk of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients.

3. The use of ~~M~~macitentan ~~for use~~ in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to claim 1 or 2, wherein the dosage of macitentan is 20 mg per day to 250 mg per day.

4. The use of ~~M~~macitentan ~~for use~~ in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to any one of claims 1 to 3, wherein the dosage of macitentan is 60 to 90 mg per day, preferably 65 to 85 mg per day, more preferably 70 to 80 mg per day and most preferably 75 mg per day.

5. The use of ~~M~~macitentan ~~for use~~ in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to any one of claims 1 to 3, wherein the dosage of macitentan is 25 to 50 mg per day, preferably 30 to 45 mg per day, more preferably 35 to 40 mg per day and most preferably 37.5 mg per day.

6. The use of ~~M~~macitentan ~~for use~~ in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to any one of claims 1 to 3, wherein the dosage of macitentan is 110 to 200 mg per day, preferably 125 to 175 mg per day, more preferably 140 to 160 mg per day and most preferably 150 mg per day.

7. The use of ~~M~~macitentan ~~for use~~ in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to any one of claims 1 to 3, wherein the dosage of macitentan is 60 to 90 mg twice per day, preferably 65 to 85 mg twice per day, more preferably 70 to 80 mg twice per day and most preferably 75 mg twice per day.

8. The use of ~~M~~macitentan ~~for use~~ in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to any one of claims 1 to 3, wherein the dosage of macitentan is 25 to 50 mg twice per day, preferably 30 to 45 mg twice per day, more preferably 35 to 40 mg twice per day and most preferably 37.5 mg twice per day.

9. The use of ~~M~~macitentan ~~for use~~ in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to any one of claims 1 to 3, wherein the dosage of macitentan is escalated from 10 mg per day, followed by 25 to 50 mg per day, preferably 37.5 mg per day, and optionally followed by 60 to 90 mg per day, preferably 75 mg per day.

10. The use of ~~M~~macitentan ~~for use~~ in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to any one of claims 1 to 3, wherein the dosage of macitentan is escalated from 10 mg per day, followed by 60 to 90 mg per day, preferably 75 mg once per day or 37.5 mg twice a day.

11. The use of ~~M~~macitentan ~~for use~~ in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to claim 9, wherein the dosage of macitentan is escalated from 10 mg once per day, preferably for 15 to 45 days; followed by 25 to 50 mg per day, preferably 37.5 mg once per day, preferably for 15 to 45 days; and optionally followed by 60 to 90 mg per day, preferably by 75 mg once per day or 37.5 mg twice per day.

12. The use of ~~M~~macitentan ~~for use~~ in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to

claim 10, wherein the dosage of macitentan is escalated from 10 mg once per day, preferably for 15 to 45 days; followed by 60 to 90 mg per day, preferably by 75 mg once per day or 37.5 mg twice per day.

13. The use of ~~M~~macitentan ~~for use~~ in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to any one of claims 1 to 4, wherein the dosage of macitentan is escalated from 25 to 50 mg per day, preferably 37.5 mg per day, preferably for 15 to 45 days; optionally followed by 60 to 90 mg per day, preferably by 75 mg per day; provided that the patient is already treated with an endothelin receptor antagonist preferably selected from bosentan and ambrisentan.

14. The use of ~~M~~macitentan ~~for use~~ in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to any one of claims 1 to 4, wherein the dosage of macitentan is 60 to 90 mg per day, preferably 75 mg per day; provided that the patient is already treated with an endothelin receptor antagonist preferably selected from bosentan and ambrisentan.

15. The use of ~~M~~macitentan ~~for use~~ in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients 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. The use of ~~M~~macitentan ~~for use~~ in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients 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 and vericiguat.

17. The use of ~~M~~macitentan ~~for use~~ in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to

claim 15 or 16, wherein macitentan is combined with tadalafil and/or selexipag or ralinepag, preferably with tadalafil and/or selexipag.

18. The use of ~~M~~macitentan ~~for use~~ in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to claim 17, 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.

19. Use of a~~A~~ pharmaceutical composition comprising macitentan in an amount of 20 mg to 300 mg and at least a pharmaceutically acceptable excipient, ~~for use~~ in the manufacture of a medicament in the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients ~~comprising macitentan and at least a pharmaceutically acceptable excipient, containing macitentan in an amount of 20 mg to 300 mg~~.

20. The use~~A pharmaceutical composition~~ according to claim 19, wherein the pharmaceutical composition~~which~~ contains macitentan in an amount of 20 mg to 250 mg, preferably 37.5 mg, 75 mg or 150 mg, more preferably 37.5 mg or 75 mg, most preferably 75 mg.

21. The use~~pharmaceutical composition~~ according to claim 19 or 20, wherein the pharmaceutical composition~~which~~ 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 usepharmaceutical composition according to any one of claims 19 to 21, wherein the pharmaceutical compositionwhich is in the form of a capsule or a tablet.

23. Use of Aaprocitentan for use in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients, wherein the dosage of aprocitentan is 100 mg per day to 1500 mg per day.

24. The use of Aaprocitentan for use in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to claim 23, wherein the treatment means the reduction of morbidity and/or mortality risk of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients.

25. The use of Aaprocitentan for use in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to claim 23 or 24, wherein the dosage of aprocitentan is 100 mg per day to 1250 mg per day.

26. The use of Aaprocitentan for use in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to any one of claims 23 to 25, wherein the dosage of aprocitentan is 300 to 450 mg per day, preferably 325 to 425 mg per day, more preferably 350 to 400 mg per day and most preferably 375 mg per day.

27. The use of Aaprocitentan for use in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to any one of claims 23 to 26, wherein the dosage of aprocitentan is 125 to 250 mg per day, preferably 150 to 225 mg per day, more preferably 175 to 200 mg per day and most preferably 187.5 mg per day.

28. The use of Aaprocitentan for use in the manufacture of a medicament for the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients, especially in Fontan-palliated patients according to any one of claims 23 to 27, wherein the dosage of aprocitentan is escalated from 50 mg per

day, followed by 125 to 250 mg per day, preferably 187.5 mg per day, and optionally followed by 300 to 450 mg per day, preferably 375 mg per day.