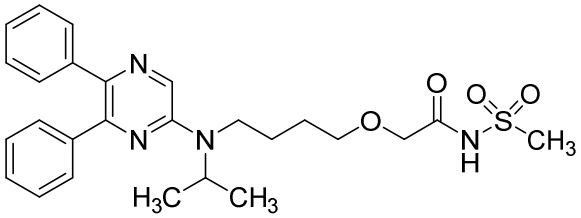
Pharmaceutical composition comprising selexipag

Technical Field

The present invention relates to pharmaceutical compositions comprising 2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}-N-(methylsulfonyl)acetamide (selexipag, NS-304, ACT-293987; hereinafter COMPOUND) which are suitable for intra venous (i.v.) administration.



Selexipag

Background of the Invention

The preparation and the medicinal use of selexipag and its active metabolite 2-(4-((5,6-diphenylpyrazin-2-yl)(isopropyl)amino)butoxy)acetic acid (MRE-269, ACT-333679) is described in WO2002/088084; WO2009/157396; WO2009/107736; WO2009/154246; WO2009/157397; WO2009/157398; WO2010/150865; WO2011/024874; Nakamura et al., Bioorg Med Chem (2007), 15, 7720-7725; Kuwano et al., J Pharmacol Exp Ther (2007), 322(3), 1181-1188; Kuwano et al., J Pharmacol Exp Ther (2008), 326(3), 691-699; O. Sitbon et al., N Engl J Med (2015), 373, 2522-33; Asaki et al., Bioorg Med Chem (2007), 15, 6692-6704; Asaki et al., J. Med. Chem. (2015), 58, 7128–7137. Certain formulations are disclosed in WO2013/024051, and WO2014/069401.

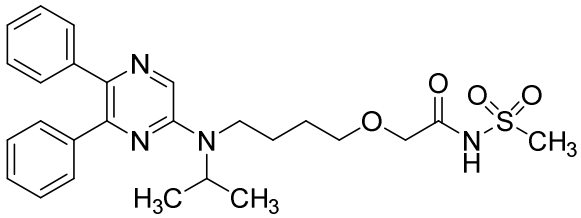
Specifically, selexipag or its active metabolite may be useful as preventive or therapeutic agent for ulcer, digital ulcer, diabetic gangrene, diabetic foot ulcer, pressure ulcer (bedsore), hypertension, pulmonary hypertension, pulmonary arterial hypertension, Fontan disease and pulmonary hypertension associated with Fontan disease, sarcoidosis and pulmonary hypertension associated with sarcoidosis, peripheral circulatory disturbance (e.g., chronic arterial occlusion, intermittent claudication, peripheral embolism, vibration syndrome, Raynaud's disease), connective tissue disease (e.g., systemic lupus erythematosus, scleroderma, mixed connective tissue disease, vasculitic syndrome), reocclusion/restenosis after percutaneous transluminal coronary angioplasty (PTCA), arteriosclerosis, thrombosis (e.g., acute-phase cerebral thrombosis, pulmonary embolism), transient ischemic attack (TIA), diabetic neuropathy, ischemic disorder (e.g., cerebral infarction, myocardial infarction), angina (e.g., stable angina, unstable angina), chronic kidney diseases including glomerulonephritis and diabetic nephropathy at any stage, allergy, bronchial asthma, restenosis after coronary intervention such as atherectomy and stent implantation, thrombocytopenia by dialysis, the diseases in which

formulations that can reproducibly be lyophilized to a stable cake and reconstituted to a controlled composition which is suitable for i.v. administration. Adsorption of active ingredient to tubings and syringes could be avoided.

Summary of the Invention

In one aspect, there is provided an aqueous pharmaceutical composition comprising:

- about 0.1 g/kg to 1 g/kg of the compound 2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}-N-(methylsulfonyl)acetamide:



;

- about 2.5 ww% to 10 ww% of a bulking agent which is glycine;
- about 0.05 ww% to 0.4 ww% of a detergent which is polysorbate 20; and
- an aqueous phosphate buffer, wherein the total amount of said phosphate buffer is about 5 mmol/kg to 20 mmol/kg;

wherein the pH of said aqueous pharmaceutical composition is between about 7 and 8.

In another aspect, there is provided a method for the preparation of a lyophilized pharmaceutical composition; said method pharmaceutical comprising the steps of:

a) preparing an aqueous pharmaceutical composition as described herein; and

b) freeze-drying said aqueous pharmaceutical composition to form a cake using a method comprising the steps of:

(i) freezing the aqueous pharmaceutical composition at a first temperature for a period sufficient to transform the liquid formulation into solid state, wherein said first temperature is in the range of about -55 °C to -25 °C;

(ii) annealing the frozen composition at a second temperature; wherein said second temperature is in the range of about -20 °C to -1 °C;

(iii) subjecting the frozen composition to a vacuum at a third temperature wherein said third temperature is in the range of about -55 °C to -25 °C; and

(iv) drying the composition in said vacuum at a fourth temperature wherein said fourth temperature is in the range of about 20 °C to 40 °C.

In yet another aspect, there is provided a lyophilized pharmaceutical composition prepared by lyophilizing an aqueous pharmaceutical composition as described herein.

In another aspect, there is provided a pharmaceutical composition as described herein for use as a medicament.

In yet another aspect, there is provided the use of a pharmaceutical composition as described herein in the manufacture of a medicament for the prevention or treatment of ulcer, digital ulcer, diabetic gangrene, diabetic foot ulcer, pulmonary hypertension, pulmonary arterial hypertension, Fontan disease and pulmonary hypertension associated with Fontan disease, sarcoidosis and pulmonary hypertension associated with sarcoidosis, peripheral circulatory disturbance, connective tissue disease, chronic kidney diseases including glomerulonephritis and diabetic nephropathy at any stage, diseases in which fibrosis of organs or tissues is involved, or respiratory diseases.

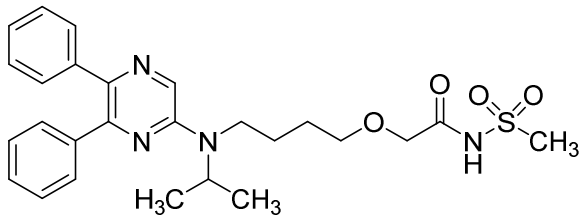
In another aspect, there is provided a method for the preparation of a reconstituted pharmaceutical composition; said method comprising the step of reconstituting the lyophilized pharmaceutical composition as described herein by adding at least one diluent to said lyophilized composition.

In yet another aspect, there is provided a reconstituted pharmaceutical composition prepared from a lyophilized pharmaceutical composition as described herein.

Detailed Description of the Invention

1) A first embodiment relates to an aqueous pharmaceutical composition comprising:

- about 0.1 g/kg to 1 g/kg, especially about 0.5 g/kg (with respect to the total weight of said aqueous pharmaceutical composition) of the compound: 2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}-N-(methylsulfonyl)acetamide:



;

- about 2.5 ww% to 10 ww% of a bulking agent which is glycine (notably about 3 ww% to 6 ww% of glycine; especially about 5 ww% of glycine) (i.e. about 25-100 g/kg; notably about 30-60 g/kg especially about 50 g/kg of glycine);
- about 0.05 ww% to 0.4 ww% of a detergent which is polysorbate 20 (notably between about 0.1 ww% and 0.3 ww% of polysorbate 20; especially about 0.1, 0.2, or 0.3 ww% of polysorbate 20) (wherein preferably about 5-40 g/kg; notably between about 10 and 30 g/kg; especially about 10, 20, or 30 g/kg of an about 10 ww% aqueous solution of polysorbate 20 is used); and
- an aqueous phosphate buffer (especially an aqueous sodium phosphate buffer (i.e. an aqueous buffer composed of H_3PO_4 and NaOH)), wherein the total amount

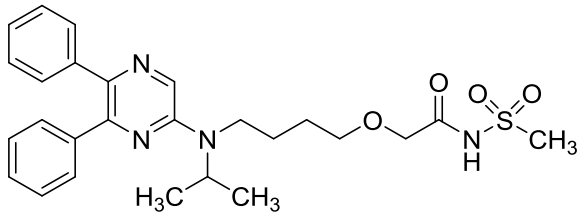
- of said phosphate buffer is about 5 mmol/kg to 20 mmol/kg (with respect to the total weight of said aqueous pharmaceutical composition), in particular about 10 mmol/kg;

wherein the pH of said aqueous pharmaceutical composition is between about 7 and 8 (notably the pH is 7.5 ± 0.3; especially 7.5 ± 0.2).

The present compositions according to embodiment 1) are liquid isotropic mixtures, which contain COMPOUND in free base form. COMPOUND may be used for the preparation of the present compositions in amorphous, or in one or more crystalline forms, or in mixtures of amorphous and crystalline form(s). Crystalline forms may be anhydrous, or solvate or hydrate forms. Such morphological forms are encompassed in the scope of COMPOUND. Preferably COMPOUND is used in crystalline form. The present compositions encompass COMPOUND in essentially pure form. The amount of COMPOUND may be adjusted

Claims

1. An aqueous pharmaceutical composition comprising:
    - about 0.1 g/kg to 1 g/kg of the compound 2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}-N-(methylsulfonyl)acetamide:



;

    - about 2.5 ww% to 10 ww% of a bulking agent which is glycine;
    - about 0.05 ww% to 0.4 ww% of a detergent which is polysorbate 20; and
    - an aqueous phosphate buffer, wherein the total amount of said phosphate buffer is about 5 mmol/kg to 20 mmol/kg;

wherein the pH of said aqueous pharmaceutical composition is between about 7 and 8.

2. An aqueous pharmaceutical composition according to claim 1; comprising:
    - about 0.5 g/kg of the compound: 2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}-N-(methylsulfonyl)acetamide;
    - about 3 ww% to 6 ww% of glycine;
    - about 0.1 ww% to 0.3 ww% of polysorbate 20; and
    - aqueous sodium phosphate buffer, wherein the concentration of said sodium phosphate buffer is about 5 mmol/kg to 20 mmol/kg;

wherein the pH of said aqueous pharmaceutical composition is 7.5 ± 0.2.

3. An aqueous pharmaceutical composition according to claim 1; comprising
    - about 0.5 g/kg of the compound: 2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}-N-(methylsulfonyl)acetamide;
    - 5 ± 0.5 ww% of glycine;
    - about 0.3 ww% of polysorbate 20; and
    - aqueous sodium phosphate buffer, wherein the concentration of said sodium phosphate buffer is about 5 mmol/kg to 20 mmol/kg;

wherein the pH of said aqueous pharmaceutical composition is 7.5 ± 0.2.

4. An aqueous pharmaceutical composition according to any one of claims 1 to 3, wherein the compound 2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}-N-(methylsulfonyl)acetamide in crystalline form is used for the preparation of said composition.

5. A method for the preparation of a lyophilized pharmaceutical composition; said method pharmaceutical comprising the steps of:

a) preparing an aqueous pharmaceutical composition according to any one of claims 1 to 4; and

b) freeze-drying said aqueous pharmaceutical composition to form a cake using a method comprising the steps of:

(i) freezing the aqueous pharmaceutical composition at a first temperature for a period sufficient to transform the liquid formulation into solid state, wherein said first temperature is in the range of about -55 °C to -25 °C;

(ii) annealing the frozen composition at a second temperature; wherein said second temperature is in the range of about -20 °C to -1 °C;

(iii) subjecting the frozen composition to a vacuum at a third temperature wherein said third temperature is in the range of about -55 °C to -25 °C; and

(iv) drying the composition in said vacuum at a fourth temperature wherein said fourth temperature is in the range of about 20 °C to 40 °C.

6. A lyophilized pharmaceutical composition prepared by lyophilizing an aqueous pharmaceutical composition according to any one of claims 1 to 4.

7. A lyophilized pharmaceutical composition according to claim 6; wherein said lyophilized pharmaceutical composition is in a container.

8. A lyophilized pharmaceutical composition according to claim 6 or 7; wherein said lyophilized pharmaceutical composition has a residual water content of less than about 2 ww%.

9. A lyophilized pharmaceutical composition according to any one of claims 6 to 8; wherein said lyophilized pharmaceutical composition is chemically stable and physically stable at room temperature and a relative humidity of about 75% or below for at least 6 month.

10. A pharmaceutical composition according to any one of claims 1 to 4 or 6 to 9 for use as a medicament.

11. Use of a pharmaceutical composition according to any one of claims 1 to 4 or 6 to 9 in the manufacture of a medicament for the prevention or treatment of ulcer, digital ulcer, diabetic gangrene, diabetic foot ulcer, pulmonary hypertension, pulmonary arterial hypertension, Fontan disease and pulmonary hypertension associated with Fontan disease, sarcoidosis and pulmonary hypertension associated with sarcoidosis, peripheral circulatory disturbance, connective tissue disease, chronic kidney diseases including glomerulonephritis and diabetic nephropathy at any stage, diseases in which fibrosis of organs or tissues is involved, or respiratory diseases.

12. A method for the preparation of a reconstituted pharmaceutical composition; said method comprising the step of reconstituting the lyophilized pharmaceutical composition according to any one of claims 6 to 9 by adding at least one diluent to said lyophilized composition.

13. A reconstituted pharmaceutical composition prepared from a lyophilized pharmaceutical composition according to any one of claims 6 to 8.

14. A reconstituted pharmaceutical composition according to claim 13; wherein said reconstituted pharmaceutical composition is in a container.

15. A reconstituted pharmaceutical composition according to claim 13 or 14; wherein said reconstituted pharmaceutical composition is reconstituted in a reconstitution time of less than about 2 minutes.

16. A reconstituted pharmaceutical composition according to claim 13 or 14; wherein said reconstituted pharmaceutical composition is reconstituted using, as diluent, water for injection or saline; wherein the total volume of said reconstituted pharmaceutical composition is between about 2 and 10 mL.

17. A reconstituted pharmaceutical composition according to any one of claims 13 to 16; wherein said reconstituted pharmaceutical composition, or a part of said reconstituted pharmaceutical composition, is further diluted; wherein said reconstituted and further diluted pharmaceutical composition contains an amount of about 4.5 μg/mL, 9 μg/mL, 13.5 μg/mL, 18 μg/mL, 22.5 μg/mL, 27 μg/mL, 31.5 μg/mL, or 36 μg/mL of the compound 2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}-N-(methylsulfonyl)acetamide.

18. A reconstituted and further diluted pharmaceutical composition according to claim 17; wherein said reconstituted and further diluted pharmaceutical composition has an osmolality of below about 1000 mOsmol/kg.