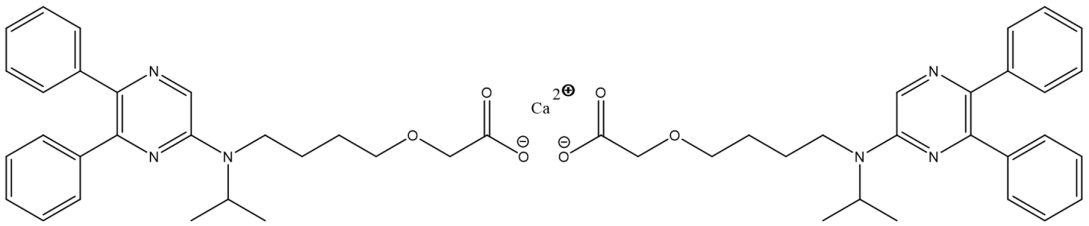
Claims

1. A pharmaceutical composition in the form of an aqueous suspension comprising

   (a) calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate of formula (I), or a pharmaceutically acceptable hydrate or solvate thereof:



Formula (I)

having a particle size distribution Dv50 of 1 to 50 µm (micrometer);

   (b) a surfactant and/or wetting agent; and

   (c) a pharmaceutically acceptable aqueous carrier at a pH in the range of 6 to 8.5.

2. The pharmaceutical composition according to claim 1, further comprising a resuspending agent.

3. The pharmaceutical composition according to claim 1 or 2, wherein the particle size distribution Dv50 is from 2 to 30 µm (micrometer).

4. The pharmaceutical composition according to any one of claims 1 to 3, wherein the surfactant and/or wetting agent is selected from the group consisting of a polysorbate, a poloxamer, an α-tocopheryl polyethylene glycol succinate, a salt of a negatively charged phospholipid, lecithin, polyvinylpyrrolidone (PVP), docusate sodium, sodium deoxycholate, sodium dodecyl sulphate (SDS), polyoxyethylene castor oil derivatives, macrogol 15 hydroxystearate, or mixtures thereof.

5. The pharmaceutical composition according to any one of claims 1 to 4, wherein the surfactant and/or wetting agent is selected from the group consisting of poloxamer 338, polysorbate 20, and Vitamin E TPGS, or a mixture thereof.

6. The pharmaceutical composition according to any one of claims 2 to 5, wherein the resuspending agent is selected from the group consisting of polyethylene glycol (PEG), carmellose sodium, and poloxamer, or a mixture thereof.

7. The pharmaceutical composition according to any one of claims 2 to 6, wherein the resuspending agent is selected from the group consisting of PEG 4000, PEG 3350, PEG 6000, PEG 8000, PEG 20000, carmellose sodium, or a mixture thereof; in particular polyethylene glycol 4000.

8. The pharmaceutical composition according to any one of claims 1 to 7, wherein the aqueous carrier comprises one or more buffering and/or pH adjusting agent(s), rendering the pH in the range of 6 to 8.5.

9. The pharmaceutical composition according to claim 8, wherein the buffering and/or pH adjusting agent(s) is/are selected from the group consisting of disodium hydrogen phosphate, citric acid, tris(hydroxymethyl)aminomethane, HCl, and NaOH, or a mixture thereof.

10. The pharmaceutical composition according to any one of claim 8 or 9, wherein the buffering agent(s) is a buffer of a buffer strength of 5 to 100 millimolar (mM).

11. The pharmaceutical composition according to any one of claims 1 to 10, wherein the pharmaceutically acceptable aqueous carrier comprises citric acid.

12. The pharmaceutical composition according to any one of claims 1 to 11, comprising by weight based on the total volume of composition:

    (a) from 2% to 50% (w/v), or from 2% to 30% (w/v), or from 2% to 15% (w/v) or from 2.5% to 10% (w/v) of calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate (or a pharmaceutically acceptable hydrate or solvate thereof; but where the w/v is calculated on the basis of its anhydrous form);

    (b) from 0.5% to 20% (w/v), or from 0.5% to 15% (w/v), or from 0.5% to 12% (w/v), or 0.5% to 10%, or from 0.5% to 8% (w/v), or from 0.5% to 7% (w/v), or from 0.5% to 6% (w/v), or from 0.5% to 5% (w/v), or from 0.5% to 4% (w/v), or from 0.5% to 3% (w/v) of a surfactant and/or wetting agent, or a mixture of surfactants and/or wetting agents;

(c) from 0% to 30% (w/v), or from 1% to 30% (w/v), or from 1% to 20% (w/v), or from 1 to 15% (w/v) or from 3 to 10% (w/v) of a resuspending agent or a mixture of resuspending agents; and

(d) from 0 to 100 mM, or from 5 to 50 mM, or from 10 to 50 mM of a buffering agent, or mixtures thereof;

(e) water for injection q.s. ad 100%.

13. A container containing the pharmaceutical composition according to any one of claims 1 to 12, wherein the container is a syringe or a vial.

14. A process for preparing a pharmaceutical composition according to any one of claims 1 to 12, said process comprising the steps of:

(a) adding a crystalline form of calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate, or a pharmaceutically acceptable hydrate or solvate thereof, to a liquid medium comprising a surfactant and/or wetting agent, optionally a resuspending agent; and a pharmaceutically acceptable aqueous carrier at a pH in the range of 6 to 8.5, to form a premix/predispersion; and

(b) subjecting the premix to mechanical means in the presence of a grinding medium to reduce the average effective particle size.

15. A process for preparing a lyophilized pharmaceutical composition, said process comprising the steps of freezing the pharmaceutical composition according to any one of claims 1 to 12, followed by a drying step comprising applying a vacuum.

16. A lyophilized pharmaceutical composition obtainable by the process according to claim 15.

17. A reconstituted pharmaceutical composition prepared from the lyophilized pharmaceutical composition according to claim 16, by adding at least one diluent.

18. A process for preparing a sterile pharmaceutical composition according to any one of claims 1 to 12, wherein the pharmaceutical composition is sterilized with autoclavation (steam sterilisation), or with gamma-irradiation; or wherein calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate is sterilised with gamma-irradiation and is used for preparing the pharmaceutical composition.

19. A sterile pharmaceutical composition obtainable by the process of claim 18.

20. Use of the pharmaceutical composition according to any one of claims 1 to 12, or 16, 17 and 19, in the preparation of a medicament for the treatment and/or prevention of a disease and/or disorder selected from the group consisting of ulcer, digital ulcer, diabetic gangrene, diabetic foot ulcer, pulmonary hypertension, Fontan disease, 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, and respiratory diseases.

21. The use according to claim 20, wherein the disease or condition is pulmonary hypertension, and the pulmonary hypertension comprises pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, pulmonary hypertension associated with Fontan disease, or pulmonary hypertension associated with sarcoidosis.

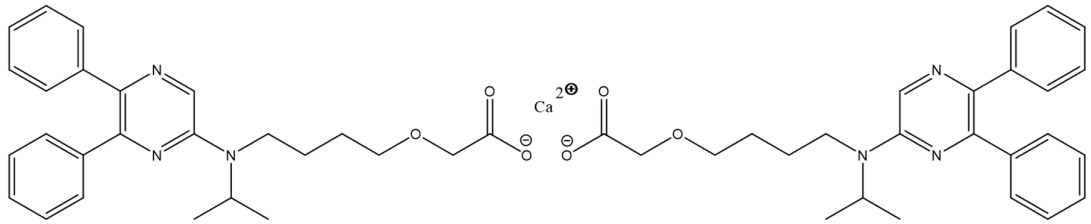
22. The use according to claim 21, wherein the disease or condition is pulmonary arterial hypertension (PAH).

23. The use according to claim 21, wherein the disease or condition is chronic thromboembolic pulmonary hypertension (CTEPH).

24. The use according to any one of claims 20 to 23, wherein the pharmaceutical composition is in the form of an intramuscular or subcutaneous injectable.

25. The use according to claim 24, wherein pharmaceutical composition is to be administered at a time interval of one week to three months.

26. Use of a pharmaceutical composition in the preparation of a long acting injectable in the treatment of and/or prevention of pulmonary hypertension, wherein the pharmaceutical composition is in the form of an aqueous suspension comprising calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate of formula (I), or a pharmaceutically acceptable hydrate or solvate thereof:



Formula (I).

27. The use according to claim 26, wherein the pulmonary hypertension comprises pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, pulmonary hypertension associated with Fontan disease, or pulmonary hypertension associated with sarcoidosis.

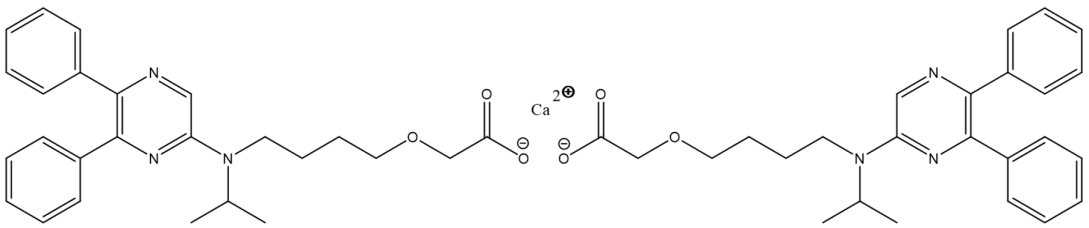
28. The use according to claim 27, wherein the pulmonary hypertension is pulmonary arterial hypertension (PAH).

29. The use according to claim 27, wherein the pulmonary hypertension is chronic thromboembolic pulmonary hypertension (CTEPH).

30. The use according to any one of claims 26 to 29, wherein the injectable is in the form of an intramuscular or subcutaneous injectable.

31. The use according to claim 30, wherein the pharmaceutical composition is to be administered at a time interval of one week to three months.

32. Microparticles of calcium;{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}acetate of formula (I), or a pharmaceutically acceptable hydrate or solvate thereof



Formula (I).

said microparticles having a particle size distribution Dv50 of 1 to 50 µm (micrometer), preferably 2 to 30 µm or 2 to 20 µm or 5 to 15 µm.

33. The microparticles according to claim 32 wherein the microparticles are suspended in an aqueous medium, which aqueous medium, in addition to water, may comprise (i) a surfactant and/or wetting agent; and optionally (ii) a resuspending agent.

34. Use of the microparticles according to claim 33 in the preparation of a medicament for the treatment of pulmonary hypertension.

35. The use according to claim 34, wherein the microparticles are to be administered by intramuscular or subcutaneous injection.

36. The use according to claim 35, wherein said intramuscular or subcutaneous injection is to be administered at a time interval of one week to three months, notably at a time interval of two weeks to one month.