[005] Betahistine is also known to have therapeutic effects in the treatment of neurological disorders such as obesity, attention deficit hyperactivity disorder, cerebrovascular disease / dementia, narcolepsy / sleep disorders, Parkinson, addiction, schizophrenia, Gilles de la Tourette syndrome, or Alzheimer's disease.

[006] In humans, betahistine is usually administered orally in the form of tablets or a solution, usually two to three times daily, up to 6 times a day. Betahistine is known for its short plasma half-life (3–4 h) which necessitates frequent administration and may lead to noncompliance, especially in elderly patients. In addition, after oral administration, betahistine is readily and almost completely absorbed from all parts of the gastro-intestinal tract. Following absorption, the drug is rapidly and almost completely metabolized into 2-pyridylacetic acid (2-PAA; which has no pharmacological activity) by monoamine oxidase. Due to its very high first pass metabolism, the absolute bioavailability of orally administered betahistine is estimated to be around 1% (SmPC). Accordingly, plasma levels of betahistine are very low.

[007] Thus, the strong first-past effect following oral administration of betahistine limits the compound's efficacy in clinical practice, and substantially higher doses may indeed be necessary in order to achieve more pronounced results. Therefore, there is a need to provide improved pharmaceutical compositions comprising betahistine, and methods of administration thereof for the treatment of otological or neurological disorders, including inner ear dysfunctions, which provides increased efficacy and allows for a reduced frequency and/or daily dosage, as well as to attain a more rapid and prolonged effect.

SUMMARY OF THE DISCLOSURE

[007a] In one aspect of the present disclosure, there is provided a pharmaceutical composition for intranasal delivery to a human patient, comprising a solution or suspension of a therapeutically effective amount of betahistine dihydrochloride, a viscosity enhancing agent, and a buffering agent, wherein the pH of the pharmaceutical composition is 4.4 to 6.4.

[007b] In another aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein, for use as a medicament.

[007c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein, for use in treating, alleviating symptoms of, or for prophylaxis of an inner ear disorder, vestibular disorder, neurotological disorder, otological disorder or

neurological disorder; wherein the composition is to be intranasally administered, and optionally wherein:

(i) the vestibular disorder is vestibular vertigo or Meniere's disease; or

(ii) the inner ear disorder is selected from tinnitus or hearing loss; or

(iii) the inner ear disorder is associated with the symptoms: hearing loss, acute hearing loss, tinnitus, nausea or dizziness.

[007d] In another aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein, for use in facilitating vestibular rehabilitation.

[007e] In a further aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein, for use in treating obesity, reducing weight gain, treating weight gain, and/or treating eating disorders, wherein the composition is to be intranasally administered; optionally where weight gain is induced by administration of antipsychotic drugs acting on histamine receptors; optionally wherein the antipsychotic drug is olanzapine.

[007f] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating, alleviating symptoms of, or for prophylaxis of an inner ear disorder, vestibular disorder, neurotological disorder, otological disorder or neurological disorder; wherein the composition is to be intranasally administered, and optionally wherein:

(i) the vestibular disorder is vestibular vertigo or Meniere's disease; or

(ii) the inner ear disorder is selected from tinnitus or hearing loss; or

(iii) the inner ear disorder is associated with the symptoms: hearing loss, acute hearing loss, tinnitus, nausea or dizziness.

[007g] In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition disclosed herein, in the manufacture of a medicament for facilitating vestibular rehabilitation.

[007h] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating obesity, reducing weight gain, treating weight gain, and/or treating eating disorders, wherein the composition is to be intranasally administered; optionally where weight gain is induced by administration of antipsychotic drugs acting on histamine receptors; optionally wherein the antipsychotic drug is olanzapine.

[008] In various examples, the present disclosure is directed to pharmaceutical compositions for intranasal delivery to a human patient, comprising a solution or suspension of therapeutically effective amount of betahistine or a pharmaceutically acceptable salt thereof and a viscosity enhancing agent.

[009] In particular examples, the present disclosure is directed to pharmaceutical compositions as described herein, wherein after a single intranasal administration to a human, the C_{max} ranges from 80-125% of: about 640 pg/mL for a 5 mg betahistine dose; about 2000 pg/mL for a 10 mg betahistine dose; about 4000 pg/mL for a 20 mg betahistine dose; or about 10500 pg/mL for a 40 mg betahistine dose.

CLAIMS

1. A pharmaceutical composition for intranasal delivery to a human patient, comprising a solution or suspension of a therapeutically effective amount of betahistine dihydrochloride, a viscosity enhancing agent, and a buffering agent, wherein the pH of the pharmaceutical composition is 4.4 to 6.4.

2. The pharmaceutical composition of claim 1, wherein the pH of the pharmaceutical composition is 4.4, 4.8, 5, 5.2, 5.4, 5.6, 5.8, 6, 6.2, or 6.4, or wherein the pH is between any of said values.

3. The pharmaceutical composition of claim 1, wherein after a single intranasal administration to a human:

   (i) the C_{max} of betahistine ranges from 80-125% of:

   640 pg/mL for a 5 mg betahistine dose;

   2000 pg/mL for a 10 mg betahistine dose;

   4000 pg/mL for a 20 mg betahistine dose; or

   10500 pg/mL for a 40 mg betahistine dose; or

   (ii) the $AUC_{0\text{-}last}$ of betahistine ranges from 80%-125%:

   210 pg*hr/mL for a 5 mg betahistine dose;

   500 pg*hr/mL for a 10 mg betahistine dose;

   1600 pg*hr/mL for a 20 mg betahistine dose; or

   3500 pg*hr/mL for a 40 mg betahistine dose; or

   (iii) the $AUC_{0\text{-}inf}$ of betahistine ranges from 80%-125%:

   275 pg*hr/mL for a 5 mg betahistine dose;

   700 pg*hr/mL for a 10 mg betahistine dose;

   1630 pg*hr/mL for a 20 mg betahistine dose; or

   3940 pg*hr/mL for a 40 mg betahistine dose; or

   (iv) the t_{max} of betahistine ranges from 0.08-0.5 hours.

4. The pharmaceutical composition of any of claims 1-3, wherein the viscosity enhancing agent is selected from the group consisting of polyvinyl pyrrolidone, polyvinyl alcohol, methylcellulose, carboxymethyl cellulose-Na, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl

methylcellulose, polyethylene-oxide, Carbopol, polyethylene glycol, propylene glycol, glycerin, alginates, carrageenan, pectins, maltodextrin, sodium starch glycolate, tragacanth gum, gum arabic, microcrystalline cellulose and combinations thereof.

5. The pharmaceutical composition of claim 4, wherein the viscosity enhancing agent is polyvinyl pyrrolidone.

6. The pharmaceutical composition of any of claims 1-5, further comprising one or more moisturizing agent; optionally wherein the one or more moisturizing agent is selected from the group consisting of glycerin, ethylene glycol, propylene glycol, propylene glycol 400, hexalene glycol, butylene glycol, dextrose, glyceryl triacetate, polydextrose, glycerol, glyceryl triacetate, sorbitol, mannitol, and combinations thereof.

7. The pharmaceutical composition of any of claims 1-6, wherein:

   (i) the composition comprises betahistine dihydrochloride at a concentration of 1 mg/mL to 1000 mg/mL, or 10 mg/mL to 400 mg/mL; or

   (ii) the composition is in the form of a unit dose comprising the betahistine dihydrochloride in an amount of 5 mg to 100 mg, 5 mg, 10 mg, 20 mg, 40 mg, or 80 mg; or

   (iii) the composition is in the form of a unit dose, comprising 1 µL to 1000 µL of the composition per unit dose.

8. The pharmaceutical composition of any of claims 1-7, wherein the composition:

   (i) is capable of being administered as a spray or aerosol; or

   (ii) is an aqueous solution; or

   (iii) comprises a lipid; or

   (iv) further comprises at least one additional pharmaceutically active agent; optionally wherein the at least one additional pharmaceutically active agent is a glutamate receptor antagonist; or

   (v) further comprises at least one enzyme inhibitor or absorption promoter.

9. The pharmaceutical composition of any of claims 1-8, wherein:

   (i) the C_{max} of betahistine in human plasma after a single intranasal dose of the composition is at least 0.5 ng/mL or at least 4 ng/mL; or

(ii) the single dose of the composition comprises 20 mg or 40 mg of betahistine dihydrochloride; or

(iii) the t_{max} of betahistine in human plasma after single intranasal dose of the composition is 0.08 h or greater or is 0.12 h or greater; or

(iv) the $AUC_{0\text{-}last}$ of betahistine in human plasma after a single intranasal dose of the composition is at least 0.2 hr*ng/mL, at least 1.5 hr*ng/mL, or at least 3.0 hr*ng/mL.

10. A pharmaceutical composition of any of claims 1-9, for use as a medicament.

11. A pharmaceutical composition of any of claims 1-9, for use in treating, alleviating symptoms of, or for prophylaxis of an inner ear disorder, vestibular disorder, neurotological disorder, otological disorder or neurological disorder; wherein the composition is to be intranasally administered, and optionally wherein:

(i) the vestibular disorder is vestibular vertigo or Meniere's disease; or

(ii) the inner ear disorder is selected from tinnitus or hearing loss; or

(iii) the inner ear disorder is associated with the symptoms: hearing loss, acute hearing loss, tinnitus, nausea or dizziness.

12. A pharmaceutical composition of any of claims 1-9, for use in facilitating vestibular rehabilitation.

13. A pharmaceutical composition of any of claims 1-9, for use in treating obesity, reducing weight gain, treating weight gain, and/or treating eating disorders, wherein the composition is to be intranasally administered; optionally where weight gain is induced by administration of antipsychotic drugs acting on histamine receptors; optionally wherein the antipsychotic drug is olanzapine.

14. The pharmaceutical composition for use according to any of claims 10-13, wherein:

(i) the composition is to be administered once a day, twice a day, three times a day, four times a day, five times a day, six times a day, seven times a day, eight times a day, nine times a day, or ten times a day; and/or

(ii) a total daily dose of the betahistine dihydrochloride is 0.01 mg/kg to 20 mg/kg bodyweight of the human patient.

15. The pharmaceutical composition for use according to any of claims 10-14, wherein:

(i) a total daily dose of the betahistine dihydrochloride is 1 to 200 mg or is 5 to 100 mg; or

(ii) the composition is to be administered in a unit dose comprising the betahistine dihydrochloride, in an amount of 1 mg to 100 mg betahistine per unit dose; or

(iii) after a single intranasal administration to a human, relative bioavailability of betahistine to be delivered intranasally is up to 10-50 times higher relative to betahistine delivered orally.

16. Use of a pharmaceutical composition of any of claims 1-9, in the manufacture of a medicament for treating, alleviating symptoms of, or for prophylaxis of an inner ear disorder, vestibular disorder, neurotological disorder, otological disorder or neurological disorder; wherein the composition is to be intranasally administered, and optionally wherein:

    (i) the vestibular disorder is vestibular vertigo or Meniere's disease; or

    (ii) the inner ear disorder is selected from tinnitus or hearing loss; or

    (iii) the inner ear disorder is associated with the symptoms: hearing loss, acute hearing loss, tinnitus, nausea or dizziness.

17. Use of a pharmaceutical composition of any of claims 1-9, in the manufacture of a medicament for facilitating vestibular rehabilitation.

18. Use of a pharmaceutical composition of any of claims 1-9, in the manufacture of a medicament for treating obesity, reducing weight gain, treating weight gain, and/or treating eating disorders, wherein the composition is to be intranasally administered; optionally where weight gain is induced by administration of antipsychotic drugs acting on histamine receptors; optionally wherein the antipsychotic drug is olanzapine.

19. The use according to any of claims 16-18, wherein:

    (i) the composition is to be administered once a day, twice a day, three times a day, four times a day, five times a day, six times a day, seven times a day, eight times a day, nine times a day, or ten times a day; and/or

    (ii) a total daily dose of the betahistine dihydrochloride is 0.01 mg/kg to 20 mg/kg bodyweight of the human patient.

20. The use according to any of claims 16-19, wherein:

(i) a total daily dose of the betahistine dihydrochloride is 1 to 200 mg or is 5 to 100 mg; or

(ii) the composition is to be administered in a unit dose comprising the betahistine dihydrochloride, in an amount of 1 mg to 100 mg betahistine per unit dose; or

(iii) after a single intranasal administration to a human, relative bioavailability of betahistine to be delivered intranasally is up to 10-50 times higher relative to betahistine delivered orally.