massively produced by the macrophages and neutrophils. Histochemistry of bone marrow aspirates and sections of spleens reveals these storage cells.

The HSR is a key homeostatic system, which is induced under conditions of metabolic stress (e.g., protein misfolding and aggregation, nutrient deprivation, oxidative or thermal stress). Its main components are the HSPs (in particular HSP70), which have significant cytoprotective properties. Heat shock protein 70 acts as molecular chaperone, assisting in the folding of newly synthesised damaged proteins, preventing protein aggregation, and targeting severely damaged proteins for degradation. Notably, the cytoprotective actions of HSP70 also include

protection against lysosomal dysfunction, cell death, and demyelination in mouse studies. Arimoclomol is a safe and well-tolerated co-inducer of HSP70 expression that acts through the activation of heat shock factor-1, the major regulator of HSP gene transcription. It is available for oral administration and show ability to cross the blood-brain barrier.

Summary

In one aspect, there is provided a use of a compound/composition comprising *N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride, and stereoisomers and acid addition salts thereof, in the manufacture of a medicament for the treatment of Gaucher disease (GD).

In another aspect, there is provided a use of a compound/composition comprising *N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride, and stereoisomers and acid addition salts thereof,

wherein the stereoisomers are selected from the group consisting of

(+)-*(R)-N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

(-)-*(S)-N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

(Z)-(R)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

(E)-(R)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

(Z)-(S)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride; and

(E)-(S)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

wherein the acid addition salts are selected from the group consisting of citrate and maleate,

in the manufacture of a medicament for the treatment of Gaucher disease (GD), wherein said Gaucher disease (GD) is Gaucher disease type 1 (GD1) or Gaucher disease type 3 (GD3).

In another aspect, there is provided a use of a compound/composition comprising *N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride, and stereoisomers and acid addition salts thereof,

wherein the stereoisomers are selected from the group consisting of

(+)-*(R)-N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

(-)-*(S)-N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

(Z)-(R)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

(E)-(R)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

(Z)-(S)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride; and

(E)-(S)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

wherein the acid addition salts are selected from the group consisting of citrate and maleate,

in the manufacture of a medicament for the treatment of at least one or more disease(s)/disease states selected from the group consisting of hepatomegaly, reducing liver size, splenomegaly, reducing spleen size, hepatosplenomegaly, anaemia, thrombocytopenia, and increasing haemoglobin in a patient.

A double-blind, randomized, placebo-controlled, phase 2 dose-finding trial in Gaucher disease (GD) type 1 and 3 patients naïve to enzyme and/or substrate replacement therapy, was conducted at seven

sites in India. A total of 39 patients were randomized 1:1:1:1 to receive placebo or 100mg, 200mg, or 400mg arimoclomol citrate (weight-adjusted) three times per day. The objective of the phase 2 study was to evaluate the response of the three dose levels of arimoclomol on various clinical and disease-specific biomarkers over a 6-month treatment period. Overall, 37 patients were included in the analysis set (2 patients excluded due to negative confirmatory GD genotype), of which 21 were type 1 GD and 16 were type 3 GD patients.

The data presented herewith show a dose-dependent effect of arimoclomol on certain disease-relevant clinical secondary endpoints, including liver and spleen size. Arimoclomol also demonstrated a relative reduction in serum chitotriosidase activity, and patients anemic at baseline showed a time-dependent increase in haemoglobin in the highest dose group.

The present disclosure provides an active pharmaceutical ingredient selected from *N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride, its

Claims

1. Use of a compound/composition comprising *N*-[2-hydroxy-3-(1- piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride, and stereoisomers and acid addition salts thereof, in the manufacture of a medicament for the treatment of Gaucher disease (GD).

2. Use of a compound/composition comprising *N*-[2-hydroxy-3-(1- piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride, and stereoisomers and acid addition salts thereof, wherein the stereoisomers are selected from the group consisting of

(+)-*(R)-N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

(-)-*(S)-N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

(Z)-(R)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

(E)-(R)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

(Z)-(S)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride; and

(E)-(S)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

wherein the acid addition salts are selected from the group consisting of citrate and maleate,

in the manufacture of a medicament for the treatment of Gaucher disease (GD), wherein said Gaucher disease (GD) is Gaucher disease type 1 (GD1) or Gaucher disease type 3 (GD3).

3. The use of a composition of claim 2, wherein composition is selected from the group consisting of

N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate,

N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride maleate;

(+)-(R)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate;

(-)-(S)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate;

(+)-(R)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride maleate;

(-)-(S)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride maleate;

(Z)-(R)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate;

(E)-(R)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate;

(Z)-(S)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate;

(E)-(S)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate;

(Z)-(R)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride maleate;

(E)-(R)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride maleate;

(Z)-(S)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride maleate; and

(E)-(S)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride maleate.

4. The use of claims 2-3, wherein said Gaucher disease (GD) is selected from the group consisting of: GD type 1 (GD1) or GD type 3 (GD3) with a deficient GBA enzyme activity below the lower limit of normal; GD type 1 (GD1) or GD type 3 (GD3) with a deficient GBA enzyme activity below the lower limit of normal; GD type 1 (GD1) with signs of brain involvement, such as with nonclinical signs of brain involvement; GD type 3 (GD3) with signs of brain involvement, such as with clinical signs of brain involvement; and GD type 3 (GD3) with at least 1 neurological symptom.

5. The use of claims 2-4, wherein the compound of the composition is to be administered one to three times a day.

6. The use of claim 5, wherein the compound is to be administered three times a day (t.i.d), at a per administration dose of 25 mg t.i.d. (75mg/day), 50 mg t.i.d. (150mg/day), 75 mg t.i.d. (225 mg/day), 100 mg t.i.d (300 mg/day), 150 mg t.i.d (450 mg/day), 200 mg t.i.d (600 mg/day), 300 mg t.i.d. (900 mg/day), or 400 mg t.i.d (1200 mg/day).

7. The use of claims 5-6, wherein the compound is to be administered to a patient with Gaucher disease in weight-adjusted dosages.

8. The use of claim 7, wherein the compound to be administered to a patient with Gaucher disease having a body weight of 10 kg to ≤ 30 kg at a dosage of 25 mg to 100 mg three times a day.

9. The use of claim 7, wherein the compound to be administered to a patient with Gaucher disease having a body weight of 30 kg to ≤ 50 kg at a dosage of 50 mg to 200 mg three times a day.

10. The use of claim 7, wherein the compound to be administered to a patient with Gaucher disease having a body weight of 50 kg to ≤ 70 kg at a dosage of 75 mg to 300 mg three times a day.

11. The use of claim 7, wherein the compound to be administered to a patient with Gaucher disease having a body weight of ≥ 70 kg at a dosage of 100 mg to about 400 mg three times a day.

12. The use of claims 5-6, wherein the compound is to be administered to a patient with Gaucher disease in age-adjusted dosages.

13. The use of claim 12, wherein the compound is to be administered to a patient with Gaucher disease aged >18 years at a dosage of 100 mg to about 400 mg three times a day.

14. Use of a compound/composition comprising *N*-[2-hydroxy-3-(1- piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride, and stereoisomers and acid addition salts thereof,

wherein the stereoisomers are selected from the group consisting of

(+)-*(R)*-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

(-)-*(S)-N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

(Z)-(R)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

(E)-(R)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

(Z)-(S)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride; and

(E)-(S)-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

wherein the acid addition salts are selected from the group consisting of citrate and maleate,

in the manufacture of a medicament for the treatment of at least one or more disease(s)/disease states selected from the group consisting of hepatomegaly, reducing liver size, splenomegaly, reducing spleen size, hepatosplenomegaly, anaemia, thrombocytopenia, and increasing haemoglobin in a patient.

15. The use of claim 14, wherein the patient has Gaucher disease.

16. The use of claim 14 or claim 15, wherein the compound of the composition is to be administered one to three times a day.

17. The use of claim 16, wherein the compound is to be administered three times a day, at a per administration dose of 25 mg t.i.d. (75mg/day), 50 mg t.i.d. (150mg/day), 75 mg t.i.d. (225 mg/day), 100 mg t.i.d (300 mg/day), 150 mg t.i.d

(450 mg/day), 200 mg t.i.d (200-600 mg/day), 300 mg t.i.d. (900 mg/day), or 400 mg t.i.d (1200 mg/day).

18. The use of claim 16, wherein the compound is to be administered three times a day, at a per administration dose of 100 mg t.i.d (300 mg/day), 200 mg t.i.d (600 mg/day), 300 mg t.i.d. (900 mg/day), or 400 mg t.i.d (1200 mg/day).