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 the use of an active pharmaceutical ingredient selected from *N*-[2-hydroxy-3-(1- piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride, its stereoisomers, or acid addition salts thereof, in the manufacture of a medicament for treating Gaucher disease (GD), wherein said GD is GD type 1 (GD1) or GD type 3 (GD3);
wherein said use is for treating hepatomegaly and/or reducing liver size in a patient with Gaucher disease,
wherein said use is for treating splenomegaly and/or reducing spleen size in a patient with Gaucher disease,
wherein said use is for treating hepatosplenomegaly and/or reducing liver size and reducing spleen size in a patient with Gaucher disease,
wherein said use is for treating anaemia in a patient with Gaucher disease,
wherein said use is for increasing haemoglobin in a patient with Gaucher disease,
wherein said use is for reducing serum chitotriosidase activity in a patient with Gaucher disease, and/or
wherein said use is for increasing glycosylsphingosine (lyso-Gb1) in a patient with Gaucher disease.

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 an active pharmaceutical ingredient selected from *N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride, its stereoisomers, or acid addition salts thereof, in the manufacture of a medicament for treating Gaucher disease (GD), wherein said GD is GD type 1 (GD1) or GD type 3 (GD3);
wherein said use is for treating hepatomegaly and/or reducing liver size in a patient with Gaucher disease,
wherein said use is for treating splenomegaly and/or reducing spleen size in a patient with Gaucher disease,
wherein said use is for treating hepatosplenomegaly and/or reducing liver size and reducing spleen size in a patient with Gaucher disease,
wherein said use is for treating anaemia in a patient with Gaucher disease,
wherein said use is for increasing haemoglobin in a patient with Gaucher disease,
wherein said use is for reducing serum chitotriosidase activity in a patient with Gaucher disease, and/or
wherein said use is for increasing glycosylsphingosine (lyso-Gb1) in a patient with Gaucher disease.

2. The use according to claim 1, wherein said Gaucher disease is GD1 or GD3 with signs of brain involvement; such as wherein said Gaucher disease is GD3 with at least one neurological symptom.

3. The use according to any of the preceding claims, wherein said splenomegaly is splenomegaly with anaemia and thrombocytopenia.

4. The use according to any of the preceding claims, wherein said hepatosplenomegaly is hepatosplenomegaly with anaemia and thrombocytopenia.

5. The use according to any of the preceding claims, wherein said patient with Gaucher disease is anaemic.

6. The use according to any of the preceding claims, wherein said use for increasing haemoglobin comprises said active pharmaceutical ingredient to be administered at a dosage of 600 mg/day (200 mg t.i.d.) or above; such as at a dosage of 600 – 900 mg/day (200-300 mg t.i.d.) or 900 – 1200 mg/day (300-400 mg t.i.d.); such as wherein said use for increasing haemoglobin comprises said active pharmaceutical ingredient to be administered at a dosage of 600 mg/day (200 mg t.i.d.) or 1200 mg/day (400 mg t.i.d.); wherein said dosages are indicated as the citrate salt.

7. The use according to any of the preceding claims, wherein said treatment dose-dependently reduces liver size; and/or wherein said treatment dose-dependently reduces spleen size; and/or wherein said treatment dose-dependently reduces chitotriosidase activity; and/or wherein said treatment time-dependently increases haemoglobin.

8. The use according to any of the preceding claims, wherein the individual has not been treated for Gaucher disease within the preceding 4 months, such as with enzyme replacement therapy and/or substrate replacement therapy; or wherein the individual to be treated has not previously been treated for Gaucher disease, such as with enzyme replacement therapy and/or substrate replacement therapy; such as wherein the individual to be treated is naive to treatment with enzyme replacement therapy and/or substrate replacement therapy.

9. The use according to any of the preceding claims, wherein said active pharmaceutical ingredient is selected from the group consisting of:

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

   an optically active stereoisomer of *N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

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

(+)-*(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;

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

an acid addition salt of *N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride,

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.

10. The use according to any of the preceding claims, wherein said active pharmaceutical ingredient is selected from the group consisting of (+)-*(R)-N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride (arimoclomol free base); and (+)-*(R)-N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate (arimoclomol citrate).

11. The use according to any one of the preceding claims, wherein the active pharmaceutical ingredient is to be administered daily, such as once daily, such as twice daily, such as three times daily; preferably wherein the active pharmaceutical ingredient is administered three times daily (t.i.d)..

12. The use according to any one of the preceding claims, wherein the active pharmaceutical ingredient is to be administered at a per administration dose of about 100 mg to about 400 mg, such as about 100 mg, 200 mg, or 400 mg; such as wherein the active pharmaceutical ingredient is to be administered at 100 mg t.i.d., such as 200 mg t.i.d., such as 400 mg t.i.d;
such as wherein the active pharmaceutical ingredient is administered at a daily dosage of 300 mg/day, of 600 mg/day, or of 1200 mg/day;
wherein said dosages are indicated as the citrate salt.

13. The use according to any one of the preceding claims, wherein the active pharmaceutical ingredient is to be administered at a daily dosage of about 100 mg/day to about 200 mg/day, such as about 200 mg/day to about 300 mg/day, such as about 300 mg/day to about 400 mg/day, such as about 400 mg/day to about 500 mg/day, such as about 500 mg/day to about 600 mg/day, such as about 700 mg/day to about 800 mg/day, such as about 800 mg/day to about 900 mg/day, such as about 900 mg/day to about 1000 mg/day, such as about 1000 mg/day to about 1100 mg/day, such as about 1100 mg/day to about 1200 mg/day, wherein said dosages are indicated as the citrate salt.

14. The use according to any of the preceding claims, wherein the active pharmaceutical ingredient is to be administered to a patient with Gaucher disease in weight-adjusted dosages or age-adjusted dosages;
such as wherein the active pharmaceutical ingredient is 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 t.i.d., 50 mg t.i.d. or 100 mg t.i.d. corresponding to a dosage of 75 mg/day, 150 mg/day or 300 mg/day;

such as wherein the active pharmaceutical ingredient is 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 t.i.d., 100 mg t.i.d. or 200 mg t.i.d. corresponding to a dosage of 150 mg/day, 300 mg/day or 600 mg/day;
such as wherein the active pharmaceutical ingredient is 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 t.i.d., 150 mg t.i.d. or 300 mg t.i.d. corresponding to a dosage of 225 mg/day, 450 mg/day or 900 mg/day;
such as wherein the active pharmaceutical ingredient is to be administered to a patient with Gaucher disease having a body weight of ≥ 70 kg at a dosage of 100 mg t.i.d., 200 mg t.i.d. or 400 mg t.i.d. corresponding to a dosage of 300 mg/day, 600 mg/day or 1200 mg/day;
such as wherein the active pharmaceutical ingredient is to be administered to a patient with Gaucher disease aged >18 years at a dosage of 100 mg t.i.d., 200 mg t.i.d. or 400 mg t.i.d. corresponding to a dosage of 300 mg/day, 600 mg/day or 1200 mg/day;
wherein said dosages are indicated as the citrate salt.

15. The use according to any of the preceding claims, wherein said patient with Gaucher disease is of age ≥ 4 and ≤ 60 years; such as wherein said patient with Gaucher disease is of age 4 to 18 years; and/or wherein said patient with Gaucher disease has a body weight of ≥ 10 kg.