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 and the acid addition salts thereof, for the manufacture of a medicament for treating or preventing Niemann Pick disease, type C (NPC) in a subject, wherein the subject has an endoplasmic reticulum (ER) type missense mutation in an *NPC* gene.

2. The use according to claim 1, wherein said active pharmaceutical ingredient is (+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride and the acid addition salts thereof.

3. The use according to any one of the preceding claims, wherein said active pharmaceutical ingredient is (+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate.

4. The use according to any one of the preceding claims, further comprising the use of an N-alkyl derivative of 1,5-dideoxy-1,5-imino-D-glucitol in which said alkyl contains from 2-8 carbon atoms, its stereoisomers and the acid addition salts thereof for the manufacture of a second medicament for combination therapy for treating or preventing Niemann Pick disease, type C (NPC) in a subject, wherein the subject has an endoplasmic reticulum (ER) type missense mutation in an *NPC* gene.

5. The use according to claim 4, wherein said second medicament is N-butyl-deoxynojirimycin (miglustat).

6. Use of (+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate (arimoclomol) and N-butyl-deoxynojirimycin (miglustat), for the manufacture of a medicament for combination therapy for treating or preventing Niemann Pick disease, type C (NPC) in a subject, wherein the subject has an ER type missense mutation in an *NPC* gene.

7. Use of an active pharmaceutical ingredient which is (+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate (arimoclomol) for the manufacture of a first medicament and use of N-butyl-deoxynojirimycin (miglustat) for the manufacture of a second medicament, wherein the first and the second medicaments are to be used in combination therapy for treating or preventing Niemann Pick disease, type C (NPC) in a subject, wherein the subject has an ER type missense mutation in an *NPC* gene.

8. The use according to any one of the preceding claims, wherein the *NPC* gene is selected from *NPC1* and *NPC2*; such as wherein the *NPC* gene is *NPC1*.

9. The use according to any one of the preceding claims, wherein the ER type missense mutation results in production of an NPC protein that is misfolded, retained at the endoplasmic reticulum (ER) and subsequently targeted for degradation; wherein the NPC protein is selected from NPC1 and NPC2; such as wherein the NPC protein is NPC1.

10. The use according to any one of the preceding claims, wherein the ER type missense mutation is selected from the group consisting of C113R, R389L, G535V, L724P, Q921P, W942C, G1034C, V378A, R404Q, H510P, Q775P, M1142T, N1156S, G1162V, R1186H, L1244P and I1061T.

11. The use according to any one of the preceding claims, wherein the subject has an *NPC1* genotype selected from the group consisting of I1061T / E1188*, I1061T / A1151T, I1061T / Q119fs, I1061T / I962fs, T1036M / I1061T, I1061T / V1141G, N968S / R1186H, N1156S / F1199sp2, Q991fs / I1061T, H1016L / I1061T, I1061T / A1192fs, I1061T / N1156S, R1186H / R1186H, P1007A / R1186H, and I1061T / D508fs.

12. The use according to any one of the preceding claims, wherein administration of the active pharmaceutical ingredient provides sustained benefit over a two-year period.

13. The use according to any one of the preceding claims, wherein the subject is about four years or older.

14. The use according to any one of the preceding claims, wherein administration of the active pharmaceutical ingredient provides sustained benefit over a two-year period, wherein the sustained benefit is characterized by the subject exhibiting a 5-domain NPCCSS score increase of no more than 1 over the two-year period.

15. The use according to any one of the preceding claims, wherein the active pharmaceutical ingredient is administered from about 100 mg/day to about 1000 mg/day; such as wherein the active pharmaceutical ingredient is (+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate and is administered from about 100 mg/day to about 1000 mg/day.

16. The use according to any one of the preceding claims, wherein the active pharmaceutical ingredient is administered at about 150 mg/day, such as about 225 mg/day, such as about 300 mg/day, such as about 450 mg/day, or such as about 600 mg/day ((+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate).

17. The use according to any one of the preceding claims, wherein the active pharmaceutical ingredient is administered three times daily (t.i.d.).

18. The use according to any one of the preceding claims, wherein the subject has a body weight of about 8 kg to about 15 kg and the active pharmaceutical ingredient is administered at a dose of about 50 mg t.i.d. (about 150 mg/day) ((+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate);
such as wherein the subject has a body weight of about 8 kg to about 15 kg and the active pharmaceutical ingredient is administered at a dose of about 75 mg t.i.d. (about 225 mg/day) ((+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate);

such as wherein the subject has a body weight of about 15 kg to about 22 kg and the active pharmaceutical ingredient is administered at a dose of about 75 mg t.i.d. (225 mg/day) ((+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate);

such as wherein the subject has a body weight of about 22 kg to about 38 kg and the active pharmaceutical ingredient is administered at a dose of about 100 mg t.i.d. (about 300 mg/day) ((+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate);

such as wherein the subject has a body weight of about 38 kg to about 55 kg and the active pharmaceutical ingredient is administered at a dose of about 150 mg t.i.d. (about 450 mg/day) ((+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate);

such as wherein the subject has a body weight of about 15 kg to about 30 kg and the active pharmaceutical ingredient is administered at a dose of about 100 mg t.i.d. (300 mg/day) ((+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate);

wherein the subject has a body weight of about 30 kg to about 55 kg and the active pharmaceutical ingredient is administered at a dose of about 150 mg t.i.d. (about 450 mg/day) ((+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate);

such as wherein the subject has a body weight of greater than about 55 kg and the active pharmaceutical ingredient is administered at a dose of about 200 mg t.i.d. (about 600 mg/day) ((+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate).

19. A method of predicting the responsiveness of a subject with Niemann Pick disease, type C (NPC) to a treatment, the method comprising:
    a) determining if the subject has an ER type missense mutation in an *NPC* gene, such as in the *NPC1* gene; and if so,
    b) predicting that the subject will respond to treatment with arimoclomol, or treatment with a combination of arimoclomol and miglustat, ;
    c) optionally further comprising use of arimoclomol for the manufacture of a medicament for treating the subject with an ER type missense mutation in an *NPC* gene; or

optionally further comprising the use of arimoclomol for the manufacture of a first medicament and the use of miglustat for the manufacture of a second medicament, wherein the first and the second medicaments are to be used in combination therapy for treating the subject with an ER type missense mutation in an *NPC* gene.

20. A method of identifying a subject with Niemann Pick disease, type C (NPC) who is likely to be responsive to a treatment, the method comprising:
    a) determining if the subject has an ER type missense mutation in an *NPC* gene, such as in the *NPC1* gene; and if so,
    b) identifying the subject as being likely to respond to treatment with arimoclomol, or treatment with a combination of arimoclomol and miglustat, ;
    c) optionally further comprising use of arimoclomol for the manufacture of a medicament for treating the subject with an ER type missense mutation in an *NPC* gene; or
    optionally further comprising the use of arimoclomol for the manufacture of a first medicament and the use of miglustat for the manufacture of a second medicament, wherein the first and the second medicaments are to be used in combination therapy for treating the subject with an ER type missense mutation in an *NPC* gene.