Claims

1. ~~An~~ 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 ~~use in a method of~~ 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 ~~active pharmaceutical ingredient for~~ 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 ~~active pharmaceutical ingredient for~~ 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 ~~active pharmaceutical ingredient for~~ use according to any one of the preceding claims, ~~said method~~ further comprising ~~administering a further active pharmaceutical ingredient selected from~~ 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 ~~active pharmaceutical ingredient for~~ use according to claim 4, wherein said ~~further active pharmaceutical ingredient~~second medicament is N-butyl-deoxynojirimycin (miglustat).

6. ~~An~~ Use of ~~active pharmaceutical ingredient, which is~~ (+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate

(arimoclomol)~~, in combination with a further active pharmaceutical ingredient, which is~~ and N-butyl-deoxynojirimycin (miglustat), for the manufacture of a medicament for combination therapy for ~~use in a method of~~ 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.

~~7. The active pharmaceutical ingredient for use according to any of the preceding claims, wherein said treatment is prophylactic, curative or ameliorating.~~

8. The ~~active pharmaceutical ingredient for~~ 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 active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the *NPC* gene is *NPC1*.~~

~~10.~~9. The ~~active pharmaceutical ingredient for~~ 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.

~~11. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the NPC protein is selected from NPC1 and NPC2.~~

~~12. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the NPC protein is NPC1.~~

~~13. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the ER type missense mutation results in a single amino-acid change.~~

~~14.~~10. The ~~active pharmaceutical ingredient for~~ 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.

~~15. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the ER type missense mutation is selected from the group consisting of I1061T, M1142T, N1156S and R1186H.~~

~~16. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the ER type missense mutation is I1061T.~~

~~17.~~11. The ~~active pharmaceutical ingredient for~~ 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.

~~18.~~12. The ~~active pharmaceutical ingredient for~~ use according to any one of the preceding claims, wherein administration of the active pharmaceutical ingredient provides sustained benefit over a two-year period.

~~19. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the active pharmaceutical ingredient is administered~~

~~for more than 1 week, such as for more than 2 weeks, such as for more than 3 weeks, such as for more than 4 weeks,~~

~~such as for more than 1 month, such as for more than 2 months, such as for more than 3 months, such as for more than 4 months, such as for more than 5 months, such as for more than 6 months,~~

~~or such as for more than 1 year, such as for more than two years, such as for more than 3 years, such as for more than 4 years, such as for 5 years or more.~~

~~20. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein treatment comprises early treatment initiation with the active pharmaceutical ingredient.~~

~~21. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the disease course is modified.~~

~~22.~~13. The ~~active pharmaceutical ingredient for~~ use according to any one of the preceding claims, wherein the subject is about four years or older.

~~23.~~14. The ~~active pharmaceutical ingredient for~~ 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.

~~24.~~15. The ~~active pharmaceutical ingredient for~~ 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.

~~25. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the active pharmaceutical ingredient is administered~~

at about 100 mg/day, such as about 125 mg/day, such as about 150 mg/day, such as about 175 mg/day, such as about 200 mg/day, such as about 225 mg/day, such as about 250 mg/day, such as about 275 mg/day, such as about 300 mg/day, such as about 325 mg/day, such as about 350 mg/day, such as about 375 mg/day, such as about 400 mg/day, such as about 425 mg/day, such as about 450 mg/day, such as about 475 mg/day, such as about 500 mg/day, such as about 525 mg/day, such as about 550 mg/day, such as about 575 mg/day, such as about 600 mg/day, such as about 625 mg/day, such as about 650 mg/day, such as about 675 mg/day, or such as about 700 mg/day ((+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate).

26.16. The active pharmaceutical ingredient for 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).

27. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the active pharmaceutical ingredient is administered in doses of about 25 mg, such as about 50 mg, such as about 75 mg, such as about 100 mg, such as about 125 mg, such as about 150 mg, such as about 175 mg, such as about 200 mg, such as about 225 mg, such as about 250 mg, such as about 275 mg, or such as about 300 mg ((+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate).

28. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the active pharmaceutical ingredient is administered in doses of about 50 mg, such as about 75 mg, such as about 100 mg, such as about 150 mg, or such as about 200 mg ((+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate).

29. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the active pharmaceutical ingredient is administered

~~at least one, at least two, at least three, at least four, at least five, at least six, or at least seven days a week.~~

~~30. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the active pharmaceutical ingredient is administered at least one time, at least two times, at least three times, at least four times, or at least five times daily.~~

~~31.~~17. The ~~active pharmaceutical ingredient for~~ use according to any one of the preceding claims, wherein the active pharmaceutical ingredient is administered three times daily (t.i.d.).

~~32. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the active pharmaceutical ingredient is administered in a dosage adjusted by patient body weight.~~

~~33.~~18. The ~~active pharmaceutical ingredient for~~ 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).

~~34. The active pharmaceutical ingredient for 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 75 mg t.i.d. (about 225 mg/day) ((+)-(*R*)-*N*-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate).~~

~~35. The active pharmaceutical ingredient for use according to any one of the preceding claims, 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).~~

~~36. The active pharmaceutical ingredient for use according to any one of the preceding claims, 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).~~

37. The active pharmaceutical ingredient for use according to any one of the preceding claims, 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).

38. The active pharmaceutical ingredient for use according to any one of the preceding claims, 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).

39. The active pharmaceutical ingredient for use according to any one of the preceding claims, 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).

40. The active pharmaceutical ingredient for use according to any one of the preceding claims, 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).

41. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the active pharmaceutical ingredient is administered orally.

42. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the active pharmaceutical ingredient is formulated for oral administration, such as in the form of tablets or capsules, or such as an oral powder, such as an oral powder suitable for suspension in a liquid, or such as as a suspension for oral administration.

43. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the administration of the active pharmaceutical ingredient reduces accumulation of unesterified cholesterol in peripheral blood mononuclear cells.

44. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the administration of the active pharmaceutical ingredient reduces accumulation of serum cholestane-triol levels.

45. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the subject is a mammal.

46. The active pharmaceutical ingredient for use according to claim 45, wherein the mammal is a human.

47. The active pharmaceutical ingredient for use according to claims 4 to 466, wherein the active pharmaceutical ingredient and the further active pharmaceutical ingredient are administered in temporal proximity.

48. The active pharmaceutical ingredient for use according to claims 4 to 47, wherein the further active pharmaceutical ingredient is administered prior to the active pharmaceutical ingredient.

49. The active pharmaceutical ingredient for use according to claims 4 to 48, wherein the active pharmaceutical ingredient is administered prior to the further active pharmaceutical ingredient.

50. The active pharmaceutical ingredient for use according to claims 4 to 49, wherein the active pharmaceutical ingredient and the further active pharmaceutical ingredient are administered simultaneously or sequentially.

51. The active pharmaceutical ingredient for use according to any one of the preceding claims, wherein the further active pharmaceutical ingredient is

~~administered for at least one year prior to an initial administration of the active pharmaceutical ingredient.~~

~~52.~~19. A method of predicting the responsiveness of a subject with Niemann Pick disease, type C (NPC) to a treatment ~~with arimoclomol~~, 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, ~~when the subject is determined to have an ER type missense mutation in an *NPC* gene,~~;

~~b)~~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.

~~53. A method of predicting the responsiveness of a subject with Niemann Pick disease, type C (NPC) to treatment with a combination of arimoclomol and miglustat, the method comprising:~~

~~a) determining if the subject has an ER type missense mutation in an *NPC* gene; and~~

~~b) predicting that the subject will respond to treatment with a combination of arimoclomol and miglustat when the subject is determined to have an ER type missense mutation in an *NPC* gene.~~

~~54.~~20. A method of identifying a subject with Niemann Pick disease, type C (NPC) who is likely to be responsive to a treatment ~~with arimoclomol~~, 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, ~~when the subject is determined to have an ER type missense mutation in an *NPC* gene~~;

~~b)~~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.

~~55. A method of identifying a subject with Niemann Pick disease, type C (NPC) who is likely to be responsive to treatment with a combination of arimoclomol and miglustat, the method comprising:~~

~~a) determining if the subject has an ER type missense mutation in an *NPC* gene; and~~

~~b) identifying the subject as being likely to respond to treatment with a combination of arimoclomol and miglustat when the subject is determined to have an ER type missense mutation in an *NPC* gene.~~

~~56. The method according to any one of claims 52 to 55, wherein the subject has an ER type missense mutation in the *NPC1* gene.~~

~~57. The method according to any one of claims 52 to 56, wherein determining an ER type missense mutation in an *NPC* gene comprises sequencing the nucleic acid isolated from a biological sample from the subject.~~

~~58. The method of any one claims 52 to 57, wherein the subject is identified as having at least one ER type missense mutation in one of the two alleles of the *NPC* gene.~~

59. The method of any one claims 52 to 58, wherein the subject is identified as having at least one ER type missense mutation in each of the two alleles of the *NPC* gene.

60. The method of any one of claims 52 to 59, wherein the subject is identified as being a compound heterozygote for the *NPC* gene.

61. The method of any of one claims 52 to 60, said method further comprising one or more steps of administering arimoclomol.

62. The method of any of one claims 52 to 61, said method further comprising one or more steps of administering arimoclomol and miglustat.

63. A method of treating or preventing Niemann Pick disease, type C (NPC) in a subject in need thereof, the method comprising administering a therapeutically effective amount 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 to a subject, wherein the subject has an ER type missense mutation in an *NPC* gene.

64. 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 the treatment of NPC in a subject, wherein the subject has an ER type missense mutation in an *NPC* gene.