SUMMARY

There is provided a method for the treatment or prevention of HIV infection in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of rilpivirine or a pharmaceutically acceptable salt thereof in the form of micro- or nanoparticles in suspension by intramuscular injection or subcutaneous injection, wherein the rilpivirine or a pharmaceutically acceptable salt thereof is administered in combination with a hyaluronidase that is administered by intramuscular injection or subcutaneous injection, and wherein the rilpivirine or pharmaceutically acceptable salt thereof and the hyaluronidase are administered intermittently at a time interval of about three months to about two years.

In a first aspect there is provided use of rilpivirine or a pharmaceutically acceptable salt thereof in the form of micro- or nanoparticles in suspension, in the manufacture of a medicament for the treatment or prevention of HIV infection in a subject in need thereof, wherein the rilpivirine or a pharmaceutically acceptable salt thereof in the form of micro- or nanoparticles in suspension is to be administered by intramuscular injection or subcutaneous injection, wherein the rilpivirine or a pharmaceutically acceptable salt thereof is to be administered in combination with a hyaluronidase that is to be administered by intramuscular injection or subcutaneous injection, and wherein the rilpivirine or a pharmaceutically acceptable salt thereof and the hyaluronidase are to be administered intermittently at a time interval of about three months to about two years.

There is also provided rilpivirine or a pharmaceutically acceptable salt thereof and a hyaluronidase for use in the treatment or prevention of HIV infection in a subject, wherein the rilpivirine or pharmaceutically acceptable salt thereof is in the form of micro- or nanoparticles in suspension, wherein the rilpivirine or pharmaceutically acceptable salt thereof and the hyaluronidase are administered to the subject by intramuscular injection or subcutaneous injection, and wherein the rilpivirine or pharmaceutically acceptable salt thereof and the hyaluronidase are administered intermittently at a time interval of about three months to about two years.

In a second aspect there is provided useof rilpivirine or a pharmaceutically acceptable salt thereof and a hyaluronidase in the manufacture of a medicament for the treatment or prevention of HIV infection, wherein the rilpivirine or a pharmaceutically acceptable salt thereof is in the form of micro- or nanoparticles in suspension, wherein the rilpivirine or pharmaceutically acceptable salt thereof and hyaluronidase are to be administered to the

subject by intramuscular injection or subcutaneous injection, and wherein the rilpivirine or pharmaceutically acceptable salt thereof and hyaluronidase are to be administered intermittently at a time interval of about three months to about two years.

There is also provided products containing rilpivirine or a pharmaceutically acceptable salt thereof and a hyaluronidase as a combined preparation for simultaneous or sequential use in the treatment or prevention of HIV infection by intramuscular injection or subcutaneous injection, wherein the rilpivirine or pharmaceutically acceptable salt thereof is in the form of micro- or nanoparticles in suspension, and wherein the rilpivirine or pharmaceutically acceptable salt thereof and the hyaluronidase are administered intermittently at a time interval of about three months to about two years.

In a third aspect there is provided products containing rilpivirine or a pharmaceutically acceptable salt thereof and a hyaluronidase as a combined preparation for simultaneous or sequential use in the treatment or prevention of HIV infection by intramuscular injection or subcutaneous injection, wherein the rilpivirine or pharmaceutically acceptable salt thereof is in the form of micro- or nanoparticles in suspension, and wherein the rilpivirine or pharmaceutically acceptable salt thereof and the hyaluronidase are to be administered intermittently at a time interval of about three months to about two years.

There is also provided a kit of parts comprising rilpivirine or a pharmaceutically acceptable salt thereof and a hyaluronidase for simultaneous or sequential use in the treatment or prevention of HIV infection by intramuscular injection or subcutaneous injection, wherein the rilpivirine or a pharmaceutically acceptable salt thereof is in the form of micro- or nanoparticles in suspension, and wherein the rilpivirine or pharmaceutically acceptable salt thereof and the hyaluronidase are administered intermittently at a time interval of about three months to about two years.

In a fourth aspect there is provided a kit of parts comprising rilpivirine or a pharmaceutically acceptable salt thereof and a hyaluronidase for simultaneous or sequential use in the treatment or prevention of HIV infection by intramuscular injection or subcutaneous injection, wherein the rilpivirine or a pharmaceutically acceptable salt thereof is in the form of micro- or nanoparticles in suspension, and wherein the rilpivirine or a pharmaceutically acceptable salt thereof and the hyaluronidase are to be administered intermittently at a time interval of about three months to about two years.

There is also provided rilpivirine or a pharmaceutically acceptable salt thereof in the form of a suspension of micro- or nanoparticles for use in the treatment or prevention of HIV infection by intramuscular injection or subcutaneous injection, wherein the rilpivirine or pharmaceutically acceptable salt thereof is administered in combination with a hyaluronidase that is administered by intramuscular injection or subcutaneous injection, and wherein the rilpivirine or pharmaceutically acceptable salt thereof and the hyaluronidase are administered intermittently at a time interval of about three months to about two years.

In a fifth aspect there is provided rilpivirine or a pharmaceutically acceptable salt thereof in the form of micro- or nanoparticles in suspension for use in the treatment or prevention of HIV infection by intramuscular injection or subcutaneous injection, wherein the rilpivirine or pharmaceutically acceptable salt thereof is to be administered in combination with a hyaluronidase that is to be administered by intramuscular injection or subcutaneous injection, and wherein the rilpivirine or pharmaceutically acceptable salt thereof and the hyaluronidase are to be administered intermittently at a time interval of about three months to about two years.

There is also provided use of rilpivirine or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating or preventing HIV infection in a subject, wherein the rilpivirine or pharmaceutically acceptable salt thereof is in the form of micro- or nanoparticles in suspension and is administered in combination with a hyaluronidase, wherein the rilpivirine or pharmaceutically acceptable salt thereof and the hyaluronidase are administered to the subject by intramuscular injection or subcutaneous injection, and wherein the rilpivirine or pharmaceutically acceptable salt thereof and the hyaluronidase are administered intermittently at a time interval of about three months to about two years.

In a sixth aspect there is provided use of rilpivirine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing HIV infection in a subject, wherein the rilpivirine or pharmaceutically acceptable salt thereof is in the form of micro- or nanoparticles in suspension and is to be administered in combination with a hyaluronidase, wherein the rilpivirine or pharmaceutically acceptable salt thereof and the hyaluronidase are to be administered to the subject by intramuscular injection or subcutaneous injection, and wherein the rilpivirine or pharmaceutically acceptable salt thereof and the hyaluronidase are to be administered intermittently at a time interval of about three months to about two years.

In a seventh aspect there is provided a combination comprising rilpivirine or a pharmaceutically acceptable salt thereof and a hyaluronidase, wherein the rilpivirine or a pharmaceutically acceptable salt thereof is in the form of micro- or nanoparticles in suspension. In an eighth aspect there is provided the combination as defined above for use in therapy.

In an ninth aspect there is provided a kit of parts comprising rilpivirine or a pharmaceutically acceptable salt thereof and a hyaluronidase, wherein the rilpivirine or a pharmaceutically acceptable salt thereof is in the form of micro- or nanoparticles in suspension.

Administration of rilpivirine in combination with a hyaluronidase by subcutaneous or intramuscular injection improves patient tolerability compared with subcutaneous or intramuscular injection administration of rilpivirine alone, in particular when large volumes are injected. The hyaluronidase may facilitate a more rapid administration of the rilpivirine as it may lower the resistance of the tissue against which the rilpivirine suspension is delivered. The hyaluronidase may reduce leakage of the rilpivirine from the site of injection by decreasing the tissue backpressure. The hyaluronidase may also allow for

delivery of larger volumes in patients with less subcutaneous tissue (or lower body mass index). The hyaluronidase may allow the use of a shorter needle.

In addition, it has surprisingly been found that the extended, sustained or prolonged release of rilpivirine into the blood plasma achieved by intramuscular injection or subcutaneous injection of a suspension of rilpivirine micro- or nanoparticles can be maintained when rilpivirine is administered with a hyaluronidase as defined herein. As discussed in more detail below in the section titled “Hyaluronidase”, hyaluronidases are used for increasing the dispersion and absorption of injected active pharmaceutical ingredients. In view of this, it is surprising that the inventors have demonstrated that administration of a hyaluronidase with rilpivirine maintains an extended, sustained or prolonged release of rilpivirine into the bloodstream.

In a tenth aspect there is provided rilpivirine or a pharmaceutically acceptable salt thereof in the form of micro- or nanoparticles in suspension, wherein the micro- or nanoparticles have a D_v90 of from about 1µm to about 10µm.

There is also provided a pharmaceutical composition comprising the rilpivirine or a pharmaceutically acceptable salt thereof as defined above.

In an eleventh aspect there is provided a pharmaceutical composition comprising rilpivirine or a pharmaceutically acceptable salt thereof in the form of micro- or nanoparticles in suspension as defined above.

In a twelfth aspect there is provided the rilpivirine or a pharmaceutically acceptable salt thereof as defined above for use in the treatment or prevention of HIV infection in a subject. In a thirteenth aspect there is provided rilpivirine or a pharmaceutically acceptable salt thereof as defined above for use in therapy.

There is also provided a method for treating or preventing HIV infection in a subject, the method comprising administering rilpivirine or a pharmaceutically acceptable salt thereof as defined above, i.e. in the form of micro- or nanoparticles in suspension, wherein the micro- or nanoparticles have a D_v90 of from about 1µm to about 10µm, to the subject.

There is also provided use of rilpivirine or a pharmaceutically acceptable salt thereof as defined above, i.e. in the form of micro- or nanoparticles in suspension, wherein the micro- or nanoparticles have a D_v90 of from about 1µm to about 10µm, for the manufacture of a medicament for treating or preventing HIV infection in a subject.

Claims

1. Use of rilpivirine or a pharmaceutically acceptable salt thereof in the form of micro- or nanoparticles in suspension, in the manufacture of a medicament for the treatment or prevention of HIV infection in a subject in need thereof,

wherein the rilpivirine or a pharmaceutically acceptable salt thereof in the form of micro- or nanoparticles in suspension is to be administered by intramuscular injection or subcutaneous injection,

wherein the rilpivirine or a pharmaceutically acceptable salt thereof is to be administered in combination with a hyaluronidase that is to be administered by intramuscular injection or subcutaneous injection, and

wherein the rilpivirine or a pharmaceutically acceptable salt thereof and the hyaluronidase are to be administered intermittently at a time interval of about three months to about two years.

2. The use according to claim 1, wherein the hyaluronidase is recombinant human hyaluronidase (e.g. rHuPH20), for example, comprising the amino acid sequence of SEQ ID NO: 1.

3. The use according to any one of the preceding claims, wherein the time interval is about three months to about one year, or about three months to about six months, or about six months to about one year, preferably wherein the time interval is about six months.

4. The use according to any one of the preceding claims, wherein the rilpivirine or a pharmaceutically acceptable salt thereof and hyaluronidase are to be administered simultaneously or sequentially.

5. The use according to any one of the preceding claims, wherein the micro- or nanoparticles have a surface modifier adsorbed to their surface.

6. The use according to claim 5, wherein the surface modifier is a poloxamer.

7. The use according to claim 6, wherein the poloxamer is poloxamer 338.

8. The use according to any one of the preceding claims, wherein the average effective particle size of the micro- or nanoparticles is less than about 1 µm or is less than about 500 nm.

9. The use according to claim 8, wherein the average effective particle size of the micro- or nanoparticles is from about 100 nm to about 300 nm.

10. The use according to claim 9, wherein the average effective particle size of the micro- or nanoparticles is from about 150 nm to about 250 nm, or from about 180 nm to about 220 nm.

11. The use according to any one of claims 1-7, wherein the micro- or nanoparticles have an average effective particle size of from about 0.2µm to about 3µm.

12. The use according to claim 11, wherein the micro- or nanoparticles have an average effective particle size of from about 1µm to about 3µm, preferably about 1.5µm to about 3µm, more preferably about 2µm to about 3µm; or from about 1µm to about 2.5µm; or of about 2.5µm.

13. The use according to any one of clauses 1-7, wherein the micro- or nanoparticles have a D_v90 of from about 2µm to about 7µm, or from about 3µm to about 6µm, or from about 3µm to about 5.5µm.

14. The use according to claim 13, wherein the micro- or nanoparticles have a D_v90 of about 5.5µm.

15. The use according to any one of the preceding claims, wherein the rilpivirine or a pharmaceutically acceptable salt thereof and the hyaluronidase are to be administered sequentially.

16. The use according to any one of the preceding claims, wherein the rilpivirine or a pharmaceutically acceptable salt thereof and hyaluronidase are to be administered in separate pharmaceutical compositions.

17. The use according to claim 16, wherein the pharmaceutical composition comprising the hyaluronidase is a solution, and the concentration of the hyaluronidase in the solution is from about 50 to about 10,000 U/mL, preferably about 2,000 U/mL.

18. The use according to any one of claims 1-14, wherein the rilpivirine or a pharmaceutically acceptable salt thereof and the hyaluronidase are to be administered as a combined pharmaceutical composition.

19. The use according to any one of the preceding claims, wherein the rilpivirine or a pharmaceutically acceptable salt thereof and the hyaluronidase are to be administered by subcutaneous injection.

20. The use according to any one of the preceding claims, wherein the suspension comprises a pharmaceutically acceptable aqueous carrier in which the rilpivirine or a pharmaceutically acceptable salt thereof is suspended.

21. The use according to any one of the preceding claims, wherein the treatment or prevention of HIV infection is treatment of HIV infection, in particular HIV type 1 (HIV-1) infection.

22. The use according to claim 21, wherein each administration of the rilpivirine or a pharmaceutically acceptable salt thereof comprises from about 2700 mg to about 5400 mg of rilpivirine or a pharmaceutically acceptable salt thereof, preferably from about 2700 mg to about 4500 mg of rilpivirine or a pharmaceutically acceptable salt thereof.

23. The use according to any one of the preceding claims, wherein the subject is a human.

24. The use according to any one of the preceding claims, wherein the rilpivirine or a pharmaceutically acceptable salt thereof is rilpivirine.

25. Use of rilpivirine or a pharmaceutically acceptable salt thereof and a hyaluronidase in the manufacture of a medicament for the treatment or prevention of HIV infection,

wherein the rilpivirine or a pharmaceutically acceptable salt thereof is in the form of micro- or nanoparticles in suspension,

wherein the rilpivirine or pharmaceutically acceptable salt thereof and hyaluronidase are to be administered to the subject by intramuscular injection or subcutaneous injection, and

wherein the rilpivirine or pharmaceutically acceptable salt thereof and hyaluronidase are to be administered intermittently at a time interval of about three months to about two years.

26. Products containing rilpivirine or a pharmaceutically acceptable salt thereof and a hyaluronidase as a combined preparation for simultaneous or sequential use in the treatment or prevention of HIV infection by intramuscular injection or subcutaneous injection,

wherein the rilpivirine or pharmaceutically acceptable salt thereof is in the form of micro- or nanoparticles in suspension, and

wherein the rilpivirine or pharmaceutically acceptable salt thereof and the hyaluronidase are to be administered intermittently at a time interval of about three months to about two years.

27. A kit of parts comprising rilpivirine or a pharmaceutically acceptable salt thereof and a hyaluronidase for simultaneous or sequential use in the treatment or prevention of HIV infection by intramuscular injection or subcutaneous injection,

wherein the rilpivirine or a pharmaceutically acceptable salt thereof is in the form of micro- or nanoparticles in suspension, and

wherein the rilpivirine or a pharmaceutically acceptable salt thereof and the hyaluronidase are to be administered intermittently at a time interval of about three months to about two years.

28. Rilpivirine or a pharmaceutically acceptable salt thereof in the form of micro- or nanoparticles in suspension for use in the treatment or prevention of HIV infection by intramuscular injection or subcutaneous injection,

wherein the rilpivirine or pharmaceutically acceptable salt thereof is to be administered in combination with a hyaluronidase that is to be administered by intramuscular injection or subcutaneous injection, and

wherein the rilpivirine or pharmaceutically acceptable salt thereof and the hyaluronidase are to be administered intermittently at a time interval of about three months to about two years.

29. Use of rilpivirine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing HIV infection in a subject,

wherein the rilpivirine or pharmaceutically acceptable salt thereof is in the form of micro- or nanoparticles in suspension and is to be administered in combination with a hyaluronidase,

wherein the rilpivirine or pharmaceutically acceptable salt thereof and the hyaluronidase are to be administered to the subject by intramuscular injection or subcutaneous injection, and

wherein the rilpivirine or pharmaceutically acceptable salt thereof and the hyaluronidase are to be administered intermittently at a time interval of about three months to about two years.

30. A combination comprising rilpivirine or a pharmaceutically acceptable salt thereof and a hyaluronidase, wherein the rilpivirine or a pharmaceutically acceptable salt thereof is in the form of micro- or nanoparticles in suspension.

31. A kit of parts comprising rilpivirine or a pharmaceutically acceptable salt thereof and a hyaluronidase, wherein the rilpivirine or a pharmaceutically acceptable salt thereof is in the form of micro- or nanoparticles in suspension.

32. Rilpivirine or a pharmaceutically acceptable salt thereof in the form of micro- or nanoparticles in suspension, wherein the micro- or nanoparticles have a D_v90 of from about 1µm to about 10µm.

33. The rilpivirine or a pharmaceutically acceptable salt thereof according to claim 32, wherein the micro- or nanoparticles have a D_v90 of from about 1µm to about 7µm, preferably from about 2µm to about 7µm; or from about 3µm to about 6µm, preferably from about 3µm to about 5.5µm.

34. The rilpivirine or a pharmaceutically acceptable salt thereof according to claim 32, wherein the micro- or nanoparticles have a D_v90 of from about 1.8µm to about 7µm and an average effective particle size of from about 0.2µm to about 3µm.

35. The rilpivirine or a pharmaceutically acceptable salt thereof according to claim 33 or claim 34, wherein the D_v90 is about 5.5µm.

36. The rilpivirine or a pharmaceutically acceptable salt thereof according to claim 34 or claim 35, wherein the average effective particle size is about 2.5µm.

37. The rilpivirine or a pharmaceutically acceptable salt thereof according to any one of claims 32-36, wherein the micro- or nanoparticles have a surface modifier adsorbed to their surface.

38. The rilpivirine or a pharmaceutically acceptable salt thereof according to claim 37, wherein the surface modifier is a poloxamer, in particular poloxamer 338.

39. The rilpivirine or a pharmaceutically acceptable salt thereof according to any one of claims 32-38, wherein the suspension comprises a pharmaceutically acceptable aqueous carrier in which the rilpivirine or a pharmaceutically acceptable salt thereof is suspended.

40. The rilpivirine or a pharmaceutically acceptable salt thereof according to any one of claims 32-39, wherein the rilpivirine or a pharmaceutically acceptable salt thereof is rilpivirine.

41. A pharmaceutical composition comprising rilpivirine or a pharmaceutically acceptable salt thereof in the form of micro- or nanoparticles in suspension as defined in any one of claims 32-40.

42. The pharmaceutical composition according to claim 41, wherein pharmaceutical composition is formulated for administration by subcutaneous or intramuscular injection.

43. The pharmaceutical composition according to claim 42, wherein the pharmaceutical composition is formulated for administration by subcutaneous injection.

44. Rilpivirine or a pharmaceutically acceptable salt thereof as defined in any one of claims 32-40, for use in the treatment or prevention of HIV infection in a subject.

45. Use of rilpivirine or a pharmaceutically acceptable salt thereof as defined in any one of claims 32-40 in the manufacture of a medicament for treating or preventing HIV infection in a subject.

46. The rilpivirine or a pharmaceutically acceptable salt thereof for use according to claim 44 or use according to claim 45, wherein the rilpivirine or a pharmaceutically acceptable salt thereof is to be administered to the subject at a time interval of about three months to about two years.

47. The rilpivirine or a pharmaceutically acceptable salt thereof for use or use according to claim 46, wherein the time interval is about three months to about six months, or about six months to about one year, preferably wherein the time interval is about 6 months.

48. The rilpivirine or a pharmaceutically acceptable salt thereof for use or use according to any one of claims 44-47, wherein the rilpivirine or a pharmaceutically acceptable salt thereof is to be administered to the subject by subcutaneous or intramuscular injection.

49. The rilpivirine or a pharmaceutically acceptable salt thereof for use or use according to claim 48, wherein the rilpivirine or a pharmaceutically acceptable salt thereof is to be administered to the subject by subcutaneous injection.

50. The rilpivirine or a pharmaceutically acceptable salt thereof for use or use according to any one of claims 44-49, wherein the treatment or prevention of HIV infection is treatment of HIV infection.

51. The rilpivirine or a pharmaceutically acceptable salt thereof for use or use according to claim 50, wherein each administration of the rilpivirine or a pharmaceutically acceptable salt thereof comprises from about 2700 mg to about 5400 mg of rilpivirine or a pharmaceutically acceptable salt thereof, preferably from about 2700 mg to about 4500 mg of rilpivirine or a pharmaceutically acceptable salt thereof.

52. The rilpivirine or a pharmaceutically acceptable salt thereof for use or use according to any one of claims 44-51, wherein the HIV infection is HIV type 1 (HIV-1) infection.

53. The rilpivirine or a pharmaceutically acceptable salt thereof for use or use according to any one of claims 44-52, wherein the subject is a human.

54. The combination according to claim 30 for use in therapy.

55. Rilpivirine or a pharmaceutically acceptable salt thereof as defined in any one of claims 32 to 40 for use in therapy.