Claims

1. A pharmaceutical composition for administration by intramuscular or subcutaneous injection, comprising a therapeutically effective amount for the long-term treatment of HIV infection, or for the long-term prevention of HIV infection in a subject at risk of being infected by HIV of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile , a salt, a stereoisomer or a stereoisomeric mixture thereof, in the form of a suspension of micro- or nanoparticles comprising:
   (a) 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]-amino]benzonitrile , a salt, a stereoisomer or a stereoisomeric mixture thereof, in micro- or nanoparticle form, having a surface modifier adsorbed to the surface thereof; and
   (b) a pharmaceutically acceptable aqueous carrier; wherein the 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile active ingredient is suspended.

2. A composition according to claim 1 wherein 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile is present in the base form.

3. A composition according to claim 2 wherein 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile is present as the E-isomer of the base form.

4. A composition according to any of claims 1 to 3, wherein the surface modifier is selected from the group of poloxamers, α-tocopheryl polyethylene glycol succinates, polyoxyethylene sorbitan fatty acid esters, and salts of negatively charged phospholipids.

5. A composition according to any of claims 1 to 3, wherein the surface modifier is selected from Pluronic™ F108 , Vitamin E TGPS, Tween™ 80, and Lipoid™ EPG

6. A composition according to any of claims 1 to 4 wherein the surface modifier is a poloxamer.

7. A composition according to claim 6 wherein the surface modifier is Pluronic™ F108.

8. A composition according to any of claims 1 to 7, wherein the average effective particle size of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile micro- or nanoparticles is below about 50 µm.

9. A composition according to any of claims 1 to 8, wherein the average effective particle size of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile micro- or nanoparticles is below about 200 nm.

10. A composition according to any of claims 1 to 9, wherein the average effective particle size of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile micro- or nanoparticles is about 130 nm.

11. A composition according to any of claims 1 to 7, wherein the average effective particle size of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile micro- or nanoparticles is in the range of 50 nm to 1000 nm.

12. A composition according to any of claims 1 to 7, wherein the average effective particle size of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile micro- or nanoparticles is in the range of 50 nm to 400 nm.

13. A composition according to any of claims 1 to 7, wherein the average effective particle size of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile micro- or nanoparticles is in the range of 150 nm to 220 nm.

14. A composition according to any of claims 1 to 13 wherein the therapeutically effective amount of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile is calculated on a basis of a dose of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile ranging from 0.5 mg/day to 50 mg/day.

15. A composition according to any of claims 1 to 13 wherein the therapeutically effective amount of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile corresponds with a monthly dose of from 15 mg to 1,500 mg.

16. A composition according to any of claims 1 to 3, comprising by weight based on the total volume of the composition:
    (a) from 3% to 50% , or from 10% to 40% , or from 10% to 30% , of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile ;
    (b) from 0.5% to 10 %, or from 0.5% to 2% of a surface modifier;
    (c) from 0% to 10%, or from 0% to 5%, or from 0% to 2%, or from 0% to 1% of one or more buffering agents;
    (d) from 0% to 10 %, or from 0% to 6% of a isotonizing agent
    (e) from 0% to 2% preservatives; and
    (f) water for injection q.s. ad 100%.

17. A composition according to any one of claims 1 to 14 wherein the composition is for administration by intramuscular or subcutaneous injection intermittently at a time interval of one week to two years.

18. A composition according to claim 17 wherein the composition is for administration by intramuscular or subcutaneous injection intermittently at a time interval of one month to one year.

19. A composition according to claim 17, wherein the composition is for administration by intramuscular or subcutaneous injection intermittently at a time interval that is in the range of one week to one month, or in the range of one month to three months, or in the range of three months to six months, or in the range of six months to twelve months, or in the range of 12 months to 24 months.

20. A composition according to claim 17, wherein the composition is for administration by intramuscular or subcutaneous injection intermittently once every two weeks, or once every month, or once every three months.

21. A composition according to claim 20 wherein the composition is for administration by intramuscular or subcutaneous injection intermittently once every month.

22. A composition according to claim 20 wherein the composition is for administration by intramuscular or subcutaneous injection intermittently once every three months.

23. The use of a pharmaceutical composition as defined in any of claims 1 to 16 for the manufacture of a medicament for the long-term treatment of HIV infection, or for the long-term prevention of HIV infection in a subject at risk of being infected by HIV.

24. The use according to claim 23 wherein the medicament is administered by intramuscular or subcutaneous injection intermittently at a time interval of one week to two years.

25. The use according to claim 23 wherein the medicament is administered by intramuscular or subcutaneous injection intermittently at a time interval of one month to one year.

26. The use according to claim 23, wherein the medicament is administered by intramuscular or subcutaneous injection intermittently at a time interval that is in the range of one week to one month, or in the range of one month to three months, or in the range of three months to six months, or in the range of six months to twelve months, or in the range of 12 months to 24 months.

27. The use according to claim 23, wherein the medicament is administered by intramuscular or subcutaneous injection intermittently once every two weeks, or once every month, or once every three months.

28. The use according to claim 27 wherein the medicament is administered by intramuscular or subcutaneous injection intermittently once every month.

29. The use according to claim 27 wherein the medicament is administered by intramuscular or subcutaneous injection intermittently once every three months.

30. The use according to claim 23 wherein the effective amount of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile in the composition is selected such that the blood plasma concentration of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile is kept during a prolonged period of time at a level ranging from 20 ng/ml to 90 ng/ml.

31. A process for preparing a pharmaceutical composition as defined in any of claims 1 to 16, comprising

(a) obtaining 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile in micronized form;

(b) adding the micronized 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile to a liquid medium to form a premix/predispersion; and

(c) subjecting the premix to mechanical means in the presence of a grinding medium to reduce the average effective particle size.

Claims

1. The use of a pharmaceutical composition for administration by intramuscular or subcutaneous injection, comprising a therapeutically effective amount of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]-amino]benzonitrile, a salt, a stereoisomer or a stereoisomeric mixture thereof, in the form of a suspension of micro- or nanoparticles comprising:
   (a) 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]-amino]benzonitrile , a salt, a stereoisomer or a stereoisomeric mixture thereof, in micro- or nanoparticle form, having a surface modifier adsorbed to the surface thereof; and
   (b) a pharmaceutically acceptable aqueous carrier; wherein the 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile active ingredient is suspended;

   for the manufacture of a medicament for the long-term treatment of HIV infection, or for the long-term prevention of HIV infection in a subject at risk of being infected by HIV, wherein the medicament is for administration by intramuscular or subcutaneous injection intermittently at a time interval of one week to two years.

2. The use of a composition according to claim 1 wherein 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile is present in the composition in the base form.

3. The use of a composition according to claim 2 wherein 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile is present in the composition as the E-isomer of the base form.

4. The use of a composition according to any one of claims 1 to 3, wherein the surface modifier in the composition is selected from the group of poloxamers, α-tocopheryl polyethylene glycol succinates, polyoxyethylene sorbitan fatty acid esters, and salts of negatively charged phospholipids.

5. The use of a composition according to any one of claims 1 to 3, wherein the surface modifier in the composition is selected from poloxamer 338, α-tocopheryl polyethylene glycol 1000 succinate, polysorbate 80, and egg phosphatidyl glycerol sodium.

6. The use of a composition according to any one of claims 1 to 4 wherein the surface modifier in the composition is a poloxamer.

7. The use of a composition according to claim 6 wherein the surface modifier in the composition is poloxamer 338.

8. The use of a composition according to any one of claims 1 to 7 wherein in the composition the relative amount (w/w) of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile to the surface modifier is in the range of 1:1 to 10:1.

9. The use of a composition according to any one of claims 1 to 8, wherein in the composition the average effective particle size of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile micro- or nanoparticles is below 50 μm.

10. The use of a composition according to any one of claims 1 to 9, wherein in the composition the average effective particle size of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile micro- or nanoparticles is below 200 nm.

11. The use of a composition according to any one of claims 1 to 10, wherein in the composition the average effective particle size of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile micro- or nanoparticles is 130 nm.

12. The use of a composition according to any one of claims 1 to 8, wherein in the composition the average effective particle size of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile micro- or nanoparticles is in the range of 50 nm to 1000 nm.

13. The use of a composition according to any one of claims 1 to 8, wherein in the composition the average effective particle size of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile micro- or nanoparticles is in the range of 50 nm to 400 nm.

14. The use of a composition according to any one of claims 1 to 8, wherein in the composition the average effective particle size of 4-[[4-[[4-(2-cyanoethenyl)-2,6-

dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile micro- or nanoparticles is in the range of 150 nm to 220 nm.

15. The use of a composition according to any one of claims 1 to 8, wherein the composition comprises 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile, a salt, a stereoisomer or a stereoisomeric mixture thereof, in nanoparticle form.

16. The use of a composition according to any one of claims 1 to 15 for the long-term prevention of HIV infection in a subject at risk of being infected, wherein the composition comprises a therapeutically effective amount for the long-term prevention of HIV infection in a subject at risk of being infected.

17. The use of a composition according to claim 16, wherein the therapeutically effective amount of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile is calculated on a basis of a dose of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile ranging from 0.5 mg/day to 50 mg/day.

18. The use of a composition according to claim 17, wherein the therapeutically effective amount is calculated on a basis of a dose of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile ranging from 1 mg/day to 10 mg/day.

19. The use of a composition according to claim 16 wherein the therapeutically effective amount of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile corresponds with a monthly dose of from 15 mg to 1,500 mg.

20. The use of a composition according to claim 19 wherein the therapeutically effective amount corresponds with a monthly dose of from 30 mg to 300 mg of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]-amino]benzonitrile.

21. The use of a composition according to claim 20 wherein the therapeutically effective amount corresponds with a monthly dose of from 60 mg to 150 mg of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]-amino]benzonitrile.

22. The use of a composition according to any one of claims 1 to 15 for the long-term treatment of HIV infection, wherein the composition comprises a therapeutically effective amount for the long-term treatment of HIV infection.

23. The use of a composition according to claim 22, wherein the therapeutically effective amount of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile is calculated on a basis of a dose of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile ranging from 5 mg/day to 50 mg/day.

24. The use of a composition according to claim 23, wherein the therapeutically effective amount is calculated on a basis of a dose of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile ranging from 10 mg/day to 25 mg/day.

25. The use of a composition according to any one of claims 1 to 3, wherein the composition comprises by weight based on the total volume of the composition:
    (a) from 3% to 50% , or from 10% to 40% , or from 10% to 30% , of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile ;
    (b) from 0.5% to 10 %, or from 0.5% to 2% of a surface modifier;
    (c) from 0% to 10%, or from 0% to 5%, or from 0% to 2%, or from 0% to 1% of one or more buffering agents;
    (d) from 0% to 10 %, or from 0% to 6% of a isotonizing agent
    (e) from 0% to 2% preservatives; and
    (f) water for injection q.s. ad 100%.

26. The use of a composition according to any one of claims 1 to 25 wherein the medicament is for administration by intramuscular or subcutaneous injection intermittently at a time interval of one month to one year.

27. The use of a composition according to any one of claims 1 to 25, wherein the medicament is for administration by intramuscular or subcutaneous injection intermittently at a time interval that is in the range of one week to one month, or in the range of one month to three months, or in the range of three months to six

months, or in the range of six months to twelve months, or in the range of 12 months to 24 months.

28. The use of a composition according to any one of claims 1 to 25, wherein the medicament is for administration by intramuscular or subcutaneous injection intermittently once every two weeks, or once every month, or once every three months.

29. The use of a composition according to claim 28 wherein the medicament is for administration by intramuscular or subcutaneous injection intermittently once every month.

30. The use of a composition according to claim 28 wherein the medicament is for administration by intramuscular or subcutaneous injection intermittently once every three months.

31. The use of a composition according to claim 27 wherein the medicament is for administration by intramuscular or subcutaneous injection intermittently once every two months

32. The use of a composition according to any one of claims 1 to 25 wherein the medicament is for administration by intramuscular or subcutaneous injection intermittently at a time interval that is in the range of 2, 3 or 4 weeks.

33. The use of a composition according to any one of claims 1 to 25 wherein the effective amount of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile in the composition is selected such that the blood plasma concentration of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile is kept during a prolonged period of time at a level ranging from 20 ng/ml to 90 ng/ml.

34. The use of a composition according to any one of claims 1 to 33 wherein the medicament is for administration by intramuscular injection.