Claims

1. A highly concentrated, stable pharmaceutical formulation of a pharmaceutically active anti-HER2 antibody comprising:

    a. about 50 to 350 mg/ml anti-HER2 antibody;

    b. about 1 to 100 mM of a buffering agent providing a pH of 5.5 ± 2.0;

    c. about 1 to 500 mM of a stabilizer or a mixture of two or more stabilizers;

    d. about 0.01 to 0.08 % of a nonionic surfactant; and

    e. an effective amount of at least one hyaluronidase enzyme.

2. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to claim 1, wherein the anti-HER2 antibody concentration is 100 to 150 mg/ml, 120 ± 18 mg/ml, about 110 mg/ml, about 120 mg/ml, or about 130 mg/ml, respectively.

3. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to claim 1 or 2, comprising more than 150 to about 16'000 U/ml of a hyaluronidase enzyme, about 2'000 U/ml, or about 12'000 U/ml, respectively.

4. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to any one of claims 1 to 3, wherein the buffering agent is at a concentration of 1 to 50 mM.

5. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to any one of claims 1 to 4, wherein the buffering agent provides a pH of 5.5 ± 0.6.

6. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to any one of claims 1 to 5, wherein the buffering agent is a histidine buffer, e.g. 20 mM histidine/HCl.

7. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to any one of claims 1 to 6, wherein the stabilizer is a saccharide, such as e.g. α,α-trehalose dihydrate or sucrose.

8. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to any one of claims 1 to 7, wherein the stabilizer is at a concentration of 15 to 250 mM or about 210 mM, respectively.

9. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to claim 7 or 8, wherein methionine is used as a second stabilizer, e.g. in a concentration of 5 to 25 mM.

10. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to any one of claims 1 to 9, wherein the nonionic surfactant is a polysorbate selected from the group consisting of polysorbate 20, polysorbate 80, and polyethylene-polypropylene copolymer.

11. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to claim 10, wherein the concentration of the polysorbate is 0.02 % (w/v), 0.04 % (w/v) or 0.06 % (w/v), respectively.

12. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to any one of claims 1 to 11, wherein the anti-HER2 antibody is selected from the group of Trastuzumab, Pertuzumab and T-DM1 or a combination of such antibodies.

13. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to any one of claims 1 to 12 which is stable upon freezing and thawing.

14. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to any one of claims 1 to 13, wherein the hyaluronidase enzyme is rHuPH20.

15. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to any one of claims 1 to 13 lacking the hyaluronidase enzyme.

16. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to any one of claims 1 to 14 for subcutaneous or intramuscular administration.

17. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to any one of claims 1 to 16 in liquid form.

18. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to any one of claims 1 to 16 in lyophilized form.

19. A highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to any one of claims 1 to 18 for the treatment of a disease or disorder amenable to treatment with an anti-HER2 antibody, such as e.g. cancer or a non-malignant disease.

20. An injection device comprising a highly concentrated, stable pharmaceutical anti-HER2 antibody formulation according to any one of claims 1 to 19.

21. The use of a formulation according to any one of claims 1 to 19 for the preparation of a medicament useful for treating a disease or disorder amenable to treatment with an anti-HER2 antibody, such as e.g. cancer or a non-malignant disease in a subject comprising administering the formulation described herein to a subject in an amount effective to treat the said disease or disorder.

22. The injection device according to claim 20 or the use according to claim 21 wherein the formulation is co-administered concomitantly or sequentially with a chemotherapeutic agent.

23. A method of treating a disease or disorder which is amenable to treatment with an anti-HER2 antibody such as cancer or a non-malignant disease in a subject comprising

administering a formulation according to any one of claims 1 to 19 to a subject in an amount effective to treat the said disease or disorder.

24. A kit comprising one or more vials containing the formulation according to any one of claims 1 to 19 and instructions for subcutaneous administration of the formulation to a patient.

25. The kit according to claim 24 further comprising an injection device for subcutaneous administration of the formulation to a patient

26. The invention as herein before described.

Claims

1. A highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection essentially consisting of:

    a. about 120 ± 18 mg/ml anti-HER2 antibody selected from the group of Trastuzumab, Pertuzumab and T-DM1 or a combination of such antibodies;

    b. about 1 to 50 mM of a histidine buffer providing a pH of 5.5 ± 0.6;

    c. about 1 to 500 mM of a stabilizer or a mixture of two or more stabilizers; and

    d. about 0.01 to 0.08 % of a nonionic surfactant.

2. A highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection according to claim 1, wherein the histidine buffer is 20 mM histidine/HCl.

3. A highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection according to claim 1 or 2, wherein the stabilizer is a saccharide.

4. A highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection according to claim 1 or 2, wherein the stabilizer is α,α-trehalose dihydrate or sucrose.

5. A highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection according to claim 1 or 2, wherein the stabilizer is 15 to 250 mM or about 210 mM α,α-trehalose dihydrate or sucrose.

6. A highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection according to any one of claims 1 to 5, wherein methionine is used as a second stabilizer.

7. A highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection according to claim 6, wherein methionine is used as a second stabilizer in a concentration of 5 to 25 mM.
8. A highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection according to any one of claims 1 to 7, wherein the nonionic surfactant is a polysorbate selected from the group consisting of polysorbate 20, polysorbate 80 and polyethylene-polypropylene copolymer.
9. A highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection according to any one of claims 1 to 8, wherein the concentration of the nonionic surfactant is 0.02 % (w/v), 0.04 % (w/v) or 0.06 % (w/v), respectively.
10. A highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection essentially consisting of 120 mg/ml Trastuzumab, 20 mM L-histidine/HCl pH 5.5, 210 mM α,α-trehalose dihydrate, 10 mM methionine and 0.04% polysorbate 20.
11. A highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection according to any one of claims 1 to 10 which is stable upon freezing and thawing.
12. A highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection according to any one of claims 1 to 11 for treating cancer or a non-malignant disease.
13. A highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection according to claim 12 wherein the cancer is gastric cancer, metastatic breast cancer or early breast cancer.

14. A highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection according to any one of claims 1 to 13 for reconstitution with 150 to about 16'000 U/ml or with about 2'000 or about 12'000 U/ml of a hyaluronidase enzyme.

15. A highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection according to any one of claims 1 to 13 for reconstitution with 150 to about 16'000 U/ml or with about 2000 or about 12000 U/ml of rHuPH20.

16. The use of a highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection according to any one of claims 1 to 14 for the preparation of a medicament useful for treating a disease or disorder amenable to treatment with an anti-HER2 antibody, optionally cancer or a non-malignant disease, in a subject comprising administering the formulation described herein to a subject in an amount effective to treat the disease or disorder.

17. The use according to claim 16 wherein the cancer is gastric cancer, metastatic breast cancer or early breast cancer.

18. An injection device comprising a highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection according to any one of claims 1 to 13.

19. The injection device according to claim 18 wherein the device provides for co-administration of the formulation with 150 to about 16'000 U/ml or with about 2'000 or about 12'000 U/ml of a hyaluronidase enzyme.

20. The injection device according to claim 18 wherein the device provides for co-administration of the formulation with 150 to about 16'000 U/ml or with about 2'000 or about 12'000 U/ml of rHuPH20.

21. The injection device according to any one of claims 18 to 20 wherein the device provides for concomitant or sequential co-administration of a chemotherapeutic agent.

22. A kit comprising one or more vials containing the highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection according to any one of claims 1 to 13 and instructions for subcutaneous administration of the formulation to a patient.

23. A kit according to claim 22 additionally containing one or more vials comprising a hyaluronidase enzyme and instructions for subcutaneous administration of the highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection and 150 to about 16'000 U/ml or about 2'000 or about 12'000 U/ml of the hyaluronidase enzyme to a patient.

24. A kit according to claim 22 additionally containing one or more vials comprising rHuPH20 and instructions for subcutaneous administration of the highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection and 150 to about 16'000 U/ml or about 2'000 or about 12'000 U/ml of rHuPH20 to a patient.

25. The kit according to claim 23 further comprising an injection device for subcutaneous administration of the highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection and 150 to about 16'000 U/ml or about 2'000 or about 12'000 U/ml of the hyaluronidase enzyme to a patient.

26. The kit according to claim 24 further comprising an injection device for subcutaneous administration of the highly concentrated, stable pharmaceutical liquid formulation of a pharmaceutically active anti-HER2 antibody for subcutaneous injection and 150 to about 16'000 U/ml or about 2'000 or about 12'000 U/ml of rHuPH20 to a patient.

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