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~~ 15 to ~~500~~ 250 mM of ~~a stabilizer or a mixture of two or more stabilizers~~ α, α-trehalose dihydrate or sucrose and 5 to 25 mM of methionine; and

   d. ~~about~~ 0.01 to 0.08 % of a nonionic surfactant, wherein said anti-HER2 antibody is Trastuzumab.

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.~~3. A highly concentrated, stable pharmaceutical ~~liquid formulation of a pharmaceutically active~~ anti-HER2 antibody formulation for subcutaneous injection according to claim 1 or 2, wherein the ~~stabilizer is~~ concentration of α,α-trehalose dihydrate or sucrose is 210 mM.

~~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.~~4. A highly concentrated, stable pharmaceutical ~~liquid formulation of a pharmaceutically active~~ anti-HER2 antibody formulation for subcutaneous injection according to any one of claims 1 to ~~7~~3, wherein the nonionic surfactant is a polysorbate selected from the group consisting of polysorbate 20, polysorbate 80 and polyethylene-polypropylene copolymer.

~~9.~~5. A highly concentrated, stable pharmaceutical ~~liquid formulation of a pharmaceutically active~~ anti-HER2 antibody formulation for subcutaneous injection according to any one of claims 1 to ~~8~~4, wherein the concentration of the ~~nonionic surfactant~~polysorbate is 0.02 % (w/v), 0.04 % (w/v) or 0.06 % (w/v), respectively.

~~10.~~6. A highly concentrated, stable pharmaceutical ~~liquid formulation of a pharmaceutically active~~ anti-HER2 antibody formulation for subcutaneous injection ~~essentially~~ according to any one of claims 1 to 5, 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.~~7. A highly concentrated, stable pharmaceutical ~~liquid formulation of a pharmaceutically active~~ anti-HER2 antibody formulation for subcutaneous injection according to any one of claims 1 to ~~11~~6 for treating cancer or a non-malignant disease.

~~13.~~8. A highly concentrated, stable pharmaceutical ~~liquid formulation of a pharmaceutically active~~ anti-HER2 antibody formulation for subcutaneous injection according to claim ~~12~~7 wherein the cancer is gastric cancer, metastatic breast cancer or early breast cancer.

~~14.~~9. A pharmaceutical formulation comprising the highly concentrated, stable pharmaceutical ~~liquid formulation of a pharmaceutically active~~ anti-HER2 antibody formulation for subcutaneous injection according to any one of claims 1 to ~~13~~ 8 for reconstitution with 150 to ~~about~~ 16'000 U/ml ~~or with about,~~ 2'000 U/ml or ~~about~~ 12'000 U/ml of a hyaluronidase enzyme.

~~15.~~10. A pharmaceutical formulation comprising the highly concentrated, stable pharmaceutical ~~liquid formulation of a pharmaceutically active~~ anti-HER2 antibody formulation for subcutaneous injection according to any one of claims 1 to ~~13~~ 8 for reconstitution with 150 to about 16'000 U/ml ~~or with about,~~ 2000 U/ml or ~~about~~ 12000 U/ml of a rHuPH20.

~~16.~~11. The use of a highly concentrated, stable pharmaceutical ~~liquid formulation of a pharmaceutically active~~ anti-HER2 antibody formulation for subcutaneous injection according to any one of claims 1 to ~~14~~ 10 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.~~12. The use according to claim ~~16~~ 11 wherein the cancer is gastric cancer, metastatic breast cancer or early breast cancer.

~~18.~~13. An injection device comprising a highly concentrated, stable pharmaceutical ~~liquid formulation of a pharmaceutically active~~ anti-HER2 antibody formulation ~~for subcutaneous injection~~ according to any one of claims 1 to ~~13~~8.

~~19.~~14. The injection device according to claim ~~18~~ 13 wherein the device provides for co-administration of the formulation with 150 to about 16'000 U/ml ~~or with about,~~ 2'000 U/ml or ~~about~~ 12'000 U/ml of a hyaluronidase enzyme.

~~20.~~15. The injection device according to claim ~~18~~ 13 wherein the device provides for co-administration of the formulation with 150 to ~~about~~ 16'000 U/ml ~~or with about,~~ 2'000 U/ml or ~~about~~ 12'000 U/ml of rHuPH20.

~~21.~~16. The injection device according to any one of claims ~~18~~ 13 to ~~20~~ 15 wherein the device provides for concomitant or sequential co-administration ~~of~~ with 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.~~

17. A kit for subcutaneous injection of a highly concentrated, stable anti-HER2 antibody formulation comprising:

A) A vial containing:

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

b. 1 to 50 mM of a histidine buffer providing a pH of 5.5 ± 0.4;

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

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

B) A vial containing 150 to 16'000 U/ml, 2000 U/ml or 12'000 U/ml of a hyaluronidase enzyme.

18. The kit according to claim 17 further comprising an injection device for subcutaneous administration of the formulation to a patient.

19. The kit according to claim 17 or 18, wherein the histidine buffer is 20 mM histidine/HCl.

20. The kit according to any one of claims 17 to 19, wherein the stabilizer is α,α-trehalose dihydrate or sucrose.

21. The kit according to any one of claims 17 to 19, wherein the stabilizer is 15 to 250 mM or 210 mM α,α-trehalose dihydrate or sucrose.

22. The kit according to any one of claims 17 to 21, wherein methionine is used as a second stabilizer.

23. The kit according to claim 22, wherein methionine is used as a second stabilizer in a concentration of 5 to 25 mM.

24. The kit according to any one of claims 17 to 23, wherein the nonionic surfactant is a polysorbate selected from the group consisting of polysorbate 20, polysorbate 80, and polyethylene-polypropylene copolymer.

25. The kit according to claim 24, wherein the concentration of the non-ionic surfactant is 0.02 % (w/v), 0.04 % (w/v) or 0.06 % (w/v).

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