Hyaluronidase products of animal origin have been used clinically for over 60 years, primarily to increase the dispersion and absorption of other co-administered drugs and for hypodermoclysis (SC injection/infusion of fluid in large volume) [Frost G. I., "Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration", *Expert Opinion on Drug Delivery*, 2007; 4: 427-440]. The details on the mechanism of action of hyaluronidases have been described in detail in the following publications: Duran-Reynolds F., "A spreading factor in certain snake venoms and its relation to their mode of action", *CR Soc Biol* Paris, 1938; 69-81; Chain E., "A mucolytic enzyme in testes extracts", Nature 1939; 977-978; Weissmann B., "The transglycosylative action of testicular hyaluronidase", *J. Biol. Chem.*, 1955; 216: 783-94; Tammi, R., Saamanen, A. M., Maibach, H. I., Tammi M., "Degradation of newly synthesized high molecular mass hyaluronan in the epidermal and dermal compartments of human skin in organ culture", *J. Invest. Dermatol.* 1991; 97:126-130; Laurent, U. B. G., Dahl, L. B., Reed, R. K., "Catabolism of hyaluronan in rabbit skin takes place locally, in lymph nodes and liver", *Exp. Physiol.* 1991; 76: 695-703; Laurent, T. C. and Fraser, J. R. E., "Degradation of Bioactive Substances: Physiology and Pathophysiology", Henriksen, J. H. (Ed) CRC Press, Boca Raton, Fla.; 1991. pp. 249-265; Harris, E. N., et al., "Endocytic function, glycosaminoglycan specificity, and antibody sensitivity of the recombinant human 190-kDa hyaluronan receptor for endocytosis (HARE)", *J. Biol. Chem.* 2004; 279:36201-36209; Frost, G. I., "Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration", *Expert Opinion on Drug Delivery*, 2007; 4: 427-440. Hyaluronidase products approved in EU countries include Hylase® "Dessau" and Hyalase®. Hyaluronidase products of animal origin approved in the US include Vitrase™, Hydase™, and Amphadase™.

Stable lyophilized antibody formulations comprising a lyoprotectant, a buffer and a surfactant have been described by Andya et al. (WO 97/04801 and U.S. Pat. Nos. 6,267,958, 6,685,940, 6,821,151, 7,060,268). WO 2006/044908 provides antibody formulations, including monoclonal antibodies formulated in histidine-acetate buffer, pH 5.5 to 6.5, preferably 5.8 to 6.2. Anti-HER2 antibody formulations are disclosed in U.S. Pat. Nos. 8,372,396; 9,017,671. Subcutaneous anti-HER2 antibody formulations and their uses are described in U.S. Pat. No. 9,345,661. Intravenous fixed dose administration of pertuzumab is disclosed in U.S. Pat. Nos. 7,449,184 and 8,404,234.

Summary

In one example, the disclosure concerns an article of manufacture comprising a single dose vial containing a single fixed dose of a HER2 antibody comprising the variable light chain and variable

heavy chain amino acid sequences of SEQ ID Nos. 7 and 8, respectively, wherein the fixed dose is about 600 mg or about 1200 mg. Preferably, the HER2 antibody is pertuzumab.

In one example, the article of manufacture comprises two single dose vials, wherein a first vial contains a single fixed dose of about 1200 mg of pertuzumab, and a second vial contains a single fixed dose of about 600 mg of pertuzumab.

In a second example, the article of manufacture comprises two single dose vials, wherein the first vial contains a single fixed dose of about 600 mg of pertuzumab and the second vial contains a single fixed dose of about 600 mg of trastuzumab.

In a third example, the article of manufacture comprises two single dose vials, wherein the first vial contains a single fixed dose of about 1200 mg of pertuzumab and a second vial comprising a single fixed dose of 600 mg of trastuzumab.

In all examples, at least one of the single dose vials may contain the fixed dose(s) in a liquid formulation for subcutaneous administration.

In all examples, the liquid formulation for subcutaneous administration may further comprise a hyaluronidase enzyme, such as recombinant human hyaluronidase (rHuPH20). rHuPH20 may be present in an amount sufficient to result in an increase in the dispersion of the pertuzumab or trastuzumab contained in the same liquid formulation during subcutaneous administration.

rHuPH2 may be present in the trastuzumab-containing liquid formulation, for example at a concentration of between about 150 U/ml and 16,000 U/ml, or at a concentration of between about 600 U/ml and about 16,000 U/ml, or at a concentration of between about 1,000 U/ml and about 2,000 U/ml, e.g. at a concentration of about 2,000 U/ml or at a concentration of at least about 600 U/mL.

rHuPH20 may be present in the pertuzumab containing liquid formulation at a concentration of between about 600 U/ml and about 2,000 U/ml, such as at a concentration of about 600 U/mL, or at a concentration of about 667 U/ml, or at a concentration of about 1,000 U/mL, or at a concentration of about 2,000 U/mL.

In another example, the single dose vial present in the article of manufacture further comprises a single fixed dose of trastuzumab.

In one example the single fixed dose of pertuzumab and the single fixed dose of trastuzumab is contained in a single liquid formulation for subcutaneous administration, where the liquid formulation may, for example contain a single fixed dose of about 600 mg of pertuzumab and a single fixed dose of about 600 mg of trastuzumab, or a single fixed dose of about 1200 mg of pertuzumab and a single fixed dose of about 600 mg of trastuzumab.

The liquid formulation comprising the fixed dose of pertuzumab and fixed dose of pertuzumab may further comprise a hyaluronidase enzyme, such as recombinant human

hyaluronidase (rHuPH20), which may be present in said liquid formulation in an amount sufficient to result in an increase in the dispersion of the pertuzumab and trastuzumab contained in the same liquid formulation during subcutaneous administration, such as at a concentration of at least about 600 U/mL, or at a concentration of between about 600 U/ml and about 2,000 U/ml, e.g. at a concentration of about 1,000 U/mL.

In some examples, the articles of manufacture herein further comprise a package insert instructing the user to administer the fixed dose(s) subcutaneously to a patient with HER2 positive cancer.

In one example, the package insert instructs the user to administer the fixed doses of pertuzumab and trastuzumab subcutaneously to a patient with HER2 positive cancer.

In another example, the package insert instructs the user to co-administer the fixed dose pertuzumab and the fixed dose of trastuzumab subcutaneously as two separate subcutaneous injections.

In a further example, the package insert instructs the user to administer the fixed dose pertuzumab co-mixed with the fixed-dose trastuzumab, as a single subcutaneous injection.

In yet another example, the package insert instructs the user to administer the fixed doses of pertuzumab and trastuzumab subcutaneously to a patient with HER2 positive cancer.

The cancer may, for example, be breast cancer, peritoneal cancer, fallopian tube cancer, lung cancer, colorectal cancer, biliary cancer or bladder cancer, such as early breast cancer (EBC) or metastatic breast cancer (MBC).

In another example, the disclosure concerns an article of manufacture comprising a 10-mL or 20-mL vial holding a single fixed dose of a HER2 antibody comprising the variable light and variable heavy amino acid sequences in SEQ ID Nos. 7 and 8, respectively, wherein the fixed dose is about 600 mg or about 1200 mg of the HER2 antibody, and a package insert instructing the user to administer the fixed dose subcutaneously to a patient with HER2 positive cancer.

In one example, the HER2 antibody is pertuzumab.

In another example, the fixed dose of pertuzumab is contained in a liquid formulation for subcutaneous administration, wherein the liquid formulation may, for example, comprise the pertuzumab at a concentration of about 100-150 mg/mL, e.g. at a concentration of about 120 mg/mL.

In various examples, the liquid formulation present in the article of manufacture further comprises recombinant human hyaluronidase (rHuPH20) in amount sufficient to result in an increase in the dispersion of the pertuzumab during subcutaneous administration, such as at a concentration of about 2,000 U/mL, or at a concentration of about 1,000 U/mL.

The article of manufacture may further comprise one of more excipients selected from the

group consisting of buffering agents, stabilizers and surfactants.

In one example, the buffering agent is suitable to adjust the pH to about 5.0 to 6.0, such as pH 5.5 to 5.7, e.g. 5.5. An exemplary buffer is a histidine buffer, such as L-histidine acetate.

The stabilizer may comprise sucrose and optionally methionine and/or trehalose

A preferred surfactant is polysorbate 20.

In a further example, the disclosure concerns an aqueous formulation for subcutaneous administration comprising pertuzumab at a concentration of about 120 mg/mL, rHuPH20 at a concentration of about1000-2000 U/mL, an L-histidine buffer to adjust to pH to about 5.5-5.7, sucrose, methionine and polysorbate 20.

In one example, the rHuPH20 is present at a concentration of about 1000 U/mL.

In another example, the rHuPH20 is present at a concentration of about 2000 U/mL.

In a further example, the of the aqueous solution is pH is 5.7.

The disclosure further concerns a liquid subcutaneous pharmaceutical composition comprising a fixed dose of pertuzumab and a fixed dose of trastuzumab co-formulated in an aqueous solution further comprising rHuPH20, a buffering agent suitable to adjust the pH to about 5.0 to 6.0, a stabilizer and a surfactant.

In one example, the buffering agent is a histidine buffer.

In another example, the buffering agent is L-histidine acetate.

In yet another example, the pH is 5.5-5.7, e.g. 5.5.

In other examples, the liquid pharmaceutical composition comprises sucrose as a stabilizer, and may further comprise methionine and/or trehalose as a stabilizer.

In one specific example, the liquid pharmaceutical composition comprises 600 mg pertuzumab at a concentration of 60 mg/ml, 600 mg trastuzumab at a concentration of 60 mg/ml, 1,000 U/mL rHuPH20, 20 mM His-HCl pH 5.5, 105 mM trehalose, 100 mM sucrose, 0.04% polysorbate 20, 10 mM methionine, and sterile water for injection up to a total volume of 10 ml, which, for example, be contained in a 15-ml vial.

In one aspect, the present disclosure provides a liquid pharmaceutical composition comprising 600 mg pertuzumab at a concentration of 60 mg/ml, 600 mg trastuzumab at a concentration of 60 mg/ml, 2,000 U/mL rHuPH20, 20 mM His-HCl pH 5.5, 105 mM trehalose, 100 mM sucrose, 0.04% polysorbate 20, 10 mM methionine, and sterile water for injection up to a total volume of 10 ml.

In another specific example, the liquid pharmaceutical composition comprises 1,200 mg pertuzumab at a concentration of 80 mg/ml, 600 mg trastuzumab at a concentration of 40 mg/ml, 1,000 U/mL rHuPH20, 20 mM His-HCl pH 5.5, 70 mM trehalose, 133 mM sucrose, 0.04% polysorbate 20, 10 mM methionine, and sterile water for injection up to a total volume of 15 ml, which may be contained in a 20-ml vial.

In another aspect, the present disclosure provides a liquid pharmaceutical composition comprising 1,200 mg pertuzumab at a concentration of 80 mg/ml, 600 mg trastuzumab at a concentration of 40 mg/ml, 2,000 U/mL rHuPH20, 20 mM His-HCl pH 5.5, 70 mM trehalose, 133 mM sucrose, 0.04% polysorbate 20, 10 mM methionine, and sterile water for injection up to a total volume of 15 ml.

In a further aspect, the present disclosure provides an article of manufacture comprising a liquid pharmaceutical composition as described herein.

The above articles of manufacture may further comprise a package insert with instructions to subcutaneously administer the liquid pharmaceutical composition contained therein to a human subject with HER2 positive cancer, such as, for example, breast cancer, peritoneal cancer, fallopian

tube cancer, lung cancer, colorectal cancer, biliary cancer and bladder cancer, e.g. early breast cancer (EBC) or metastatic breast cancer (MBC).

In yet a further aspect, the present disclosure provides use of a HER2 antibody comprising the variable light and variable heavy amino acid sequences in SEQ ID Nos. 7 and 8, respectively, in the manufacture of a medicament for treating HER2 positive cancer, wherein the HER2 antibody is to be administered subcutaneously at a fixed loading dose of 1200 mg followed by at least one maintenance dose of 600 mg.

In a further example, the disclosure concerns a method for treating cancer comprising subcutaneously administering to a human subject with a HER2 positive cancer one or more fixed dose(s) of a HER2 antibody comprising the variable light and variable heavy amino acid sequences in SEQ ID Nos. 7 and 8, respectively, in an amount effective to treat the cancer, wherein the fixed dose is about 600 mg and/or about 1200 mg.

The HER2 antibody preferably is pertuzumab.

In one example, the method comprises administering to the human subject pertuzumab at a fixed loading dose of about 1200 mg followed by at least one maintenance dose of about 600 mg.

In a second example, the administration of the loading dose is followed by administration of multiple maintenance doses.

In a third example, the first maintenance dose of pertuzumab is administered to the human subject approximately two weeks or approximately three weeks after administration of the loading dose of pertuzumab.

In further examples, the fixed doses of pertuzumab are administered to the human subject approximately every 2 weeks or approximately every 3 weeks.

The cancer may be HER2 positive cancer, such as breast cancer, peritoneal cancer, fallopian tube cancer, lung cancer, colorectal cancer, biliary cancer and bladder cancer, e.g. early breast cancer (EBC) or metastatic breast cancer (MBC).

Optionally, the method may further comprise administering a second therapeutic agent to the patient, such as a different HER2 antibody, e.g. trastuzumab, or a chemotherapeutic agent.

In one example, the fixed dose pertuzumab is administered subcutaneously in combination with subcutaneously administered trastuzumab.

In another example, the fixed dose pertuzumab and the trastuzumab are co-administered subcutaneously as two separate subcutaneous injections.

In yet another example, the fixed dose pertuzumab is co-mixed with fixed dose trastuzumab, and administered as a single subcutaneous injection.

In a further example, the fixed dose pertuzumab and fixed dose trastuzumab are administered as a single co-formulation for subcutaneous administration, such as any of the co-formulations described hereinabove and throughout the disclosure.

The chemotherapeutic agent, if administered, may, for example, be a taxane and/or an anthracycline, such as paclitaxel, docetaxel, daunorubicin, doxorubicin, and/or epirubicin.

WHAT IS CLAIMED IS:

1. A liquid pharmaceutical composition comprising 600 mg pertuzumab at a concentration of 60 mg/ml, 600 mg trastuzumab at a concentration of 60 mg/ml, 2,000 U/mL rHuPH20, 20 mM His-HCl pH 5.5, 105 mM trehalose, 100 mM sucrose, 0.04% polysorbate 20, 10 mM methionine, and sterile water for injection up to a total volume of 10 ml.

2. The liquid pharmaceutical composition of claim 1, contained in a 15-ml vial.

3. A liquid pharmaceutical composition comprising 1,200 mg pertuzumab at a concentration of 80 mg/ml, 600 mg trastuzumab at a concentration of 40 mg/ml, 2,000 U/mL rHuPH20, 20 mM His-HCl pH 5.5, 70 mM trehalose, 133 mM sucrose, 0.04% polysorbate 20, 10 mM methionine, and sterile water for injection up to a total volume of 15 ml.

4. The liquid pharmaceutical composition of claim 3, contained in a 20-ml vial.

5. An article of manufacture comprising a liquid pharmaceutical composition of any one of claims 1 to 4.

6. The article of manufacture of claim 5, further comprising a package insert with instructions to subcutaneously administer the liquid pharmaceutical composition contained therein to a human subject with HER2 positive cancer.

7. The article of manufacture of claim 6, wherein the HER2 positive cancer is selected from the group consisting of breast cancer, peritoneal cancer, fallopian tube cancer, lung cancer, colorectal cancer, biliary cancer and bladder cancer.

8. The article of manufacture of claim 7, wherein the cancer is breast cancer.

9. The article of manufacture of claim 8, wherein the breast cancer is early breast cancer (EBC) or metastatic breast cancer (MBC).

10. Use of a HER2 antibody comprising the variable light and variable heavy amino acid sequences in SEQ ID Nos. 7 and 8, respectively, in the manufacture of a medicament for treating HER2 positive cancer, wherein the HER2 antibody is to be administered subcutaneously at a fixed loading dose of 1200 mg followed by at least one maintenance dose of 600 mg.

11. The use of claim 10, wherein the HER2 antibody is pertuzumab.

12. The use of claim 10 or 11, wherein the administration of the loading dose is to be followed by administration of multiple maintenance doses.

13. The use of claim 11 or 12, wherein the first maintenance dose of pertuzumab is to be administered to said human subject approximately two weeks or approximately three weeks after administration of the loading dose of pertuzumab.

14. The use of any one of claims 11 to 13, wherein the fixed doses of pertuzumab are to be administered to said human subject approximately every 2 weeks or approximately every 3 weeks.

15. The use of claim 14, wherein the fixed doses of pertuzumab are to be administered approximately every 3 weeks.

16. The use of claim 10, wherein the HER2 positive cancer is selected from the group consisting of breast cancer, peritoneal cancer, fallopian tube cancer, lung cancer, colorectal cancer, biliary cancer and bladder cancer.

17. The use of claim 16, wherein the cancer is breast cancer.

18. The use of claim 17, wherein the breast cancer is early breast cancer (EBC) or metastatic breast cancer (MBC).

19. The use of any one of claims 10 to 18, wherein a second therapeutic agent is to be administered to the patient.

20. The use of claim 19, wherein the second therapeutic agent is a different HER2 antibody.

21. The use of claim 20, wherein the HER2 antibody is trastuzumab.

22. The use of claim 21, wherein the fixed dose pertuzumab is to be administered subcutaneously in combination with subcutaneously administered trastuzumab.

23. The use of claim 22, wherein the fixed dose pertuzumab and the trastuzumab are to be co-administered subcutaneously as two separate subcutaneous injections.

24. The use of claim 22, wherein the fixed dose pertuzumab is co-mixed with fixed dose trastuzumab, and is to be administered as a single subcutaneous injection.

25. The use of claim 22, wherein fixed dose pertuzumab and fixed dose trastuzumab are to be administered as a single co-formulation for subcutaneous administration.

26. The use of claim 25, wherein the co-formulation is a liquid pharmaceutical composition of any one of claims 1 to 4.

27. The use of claim 19, wherein the further therapeutic agent is a chemotherapeutic agent.

28. The use of claim 27, wherein the chemotherapeutic agent is taxane and anthracycline.

29. The use of claim 28, wherein the taxane is paclitaxel or docetaxel.

30. The use of claim 28, wherein the anthracycline comprises daunorubicin, doxorubicin, or epirubicin.