RADIOPHARMACEUTICAL AND METHODS

Related Applications

This application claims the benefit of U.S. Provisional Application No. 63/315,974 filed March 2, 2022 and U.S. Provisional Application No. 63/316,381 filed March 3, 2022. The entire contents of the above-referenced applications are incorporated by reference herein.

Field of the Invention

The radiopharmaceutical ^{177}Lu-DOTATATE (^{177}Lu-octreotate) and a pharmaceutical composition thereof are provided. Further provided are methods of preparing ^{177}Lu-DOTATATE compound and pharmaceutical compositions that include ^{177}Lu-DOTATATE.

Background of the Invention

Radiopharmaceuticals have been used for a variety of therapeutic and diagnostic indications. Among others, radiolabeled molecules have been useful to treat various malignant tumors.

Use of these agents presents certain challenges, including with respect to stability and shelf-life. In particular, therapeutic compositions comprising a radionuclide may undergo radiolysis during preparation and storage. During radiolysis, radionuclide emissions may react with other groups of the pharmaceutical agent thereby resulting in decomposition of the agent as well as undesired effects.

It thus would be desirable to have additional and improved radiopharmaceutical agents.

Summary

In a first aspect of the present disclosure, there is provided a pharmaceutical composition comprising:

(a) a complex of lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE); and

(b) one or more ascorbate compounds, wherein the composition is substantially or completely free of stabilizer compounds other than the one or more ascorbate compounds.

In another aspect of the present disclosure, there is provided a method for preparing the pharmaceutical composition as disclosed herein, comprising the steps of:

a) admixing lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE) in aqueous solution in the presence of one or more ascorbate compounds in a concentration of 40 mg/mL or less, in the substantial or complete absence of a second stabilizing agent, and

b) heating the admixture, thereby forming an aqueous solution comprising a complex of lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE);

c) mixing the aqueous solution of step b) with an aqueous formulation composition comprising one or more ascorbate compounds in the substantial or complete absence of a second stabilizing agent.

In yet another aspect of the present disclosure, there is provided a use of the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating cancer in a subject in need thereof.

In a further aspect of the present disclosure, there is provided a single dosage kit comprising the pharmaceutical composition as disclosed herein.

In another aspect of the present disclosure, there is provided a multiple dosage kit comprising the pharmaceutical composition as disclosed herein

In yet another aspect of the present disclosure, there is provided a sealed container comprising the pharmaceutical composition as disclosed herein.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition as disclosed herein for use in therapy.

We now provide, *inter alia*, radiopharmaceutical ^{177}Lu-DOTATATE compound, methods of preparing the compound, and pharmaceutical compositions and methods of treatment including ^{177}Lu-DOTATATE.

We have now found, inter alia, 1) new methods to produce high purity ^{177}Lu-DOTATATE including with high levels of ^{177}Lu incorporation, mild reaction temperatures and/or reduced reaction times and 2) new ^{177}Lu-DOTATATE pharmaceutical compositions that maintain radiochemical purity for extended storage times following preparation (e.g. >90 or 95%, 3, 4 or 5 days or more, 25^{o}C).

The preferred methods and pharmaceutical compositions include one or more ascorbate compounds such as ascorbic acid, but do not contain other stabilizer agents. In particular examples, the present methods and pharmaceutical compositions are substantially or completely free of a gentisate compound such as gentisic acid.

As referred to herein, one or more gentisate compounds would be substantially absent (or an admixture comprising lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA would be substantially free of gentisate compound(s)) if one or more gentisate compounds are present in an amount of less than 10, 8, 5, 4, 3, 2, 1, 0.5, 0.25, or 0.1 weight percent relative to the weight amount of one or more ascorbate compounds. In certain examples, a gentisate compound such as gentisic acid can be completely absent (e.g. effectively undetectable (e.g. by HPLC or other analysis) including by such analysis zero weight percent relative to the weight amount of one or more ascorbate compounds).

More particularly, in one example, pharmaceutical compositions are provided that comprise: (a) a complex of lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE); and (b) one or more or more ascorbate compounds, in the substantial or complete absence of a gentisate compound such as gentisic acid. Such pharmaceutical composition may comprise one or more other components such as one or more sequestering agents, an organic or inorganic base, salt and/or buffering agents.

In a further example, pharmaceutical compositions are provided that comprise: (a) a complex of lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE); and (b) one or more or more ascorbate compounds such as ascorbic acid, in the substantial or complete absence of a gentisate compound (e.g. such as gentisic acid) or additional stabilizer compounds other than an ascorbate compound. Such pharmaceutical composition may comprise one or more other components such as one or more sequestering agents, organic or inorganic base, a salt such as NaCl, and/or one or more buffering agents.

In one preferred example, pharmaceutical compositions are provided that consist essentially of: (a) a complex of lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE); and (b) one or more or more ascorbate compounds such as ascorbic acid, in the substantial or complete absence of a gentisate compound such as gentisic acid. Such pharmaceutical composition may comprise one or more other components such as one or more sequestering agents, organic or inorganic base, a salt such as NaCl, and/or one or more buffering agents.

In certain examples, suitably, the complex of lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE) is present in an amount of at least 5, 10, 15, 20, 25 or 30 mCi/mL.

In certain preferred examples, one or more ascorbate compounds such as ascorbic acid are present in a pharmaceutical composition in an amount of 1 mg/mL or greater.

In certain preferred examples, one or more ascorbate compounds such as ascorbic acid are present in a pharmaceutical composition in an amount of 2 mg/mL or greater.

In certain preferred examples, one or more ascorbate compounds such as ascorbic acid are present in a pharmaceutical composition in an amount of 3 mg/mL or greater.

In certain preferred examples, one or more ascorbate compounds such as ascorbic acid are present in a pharmaceutical composition in an amount of 4 mg/mL or greater.

In certain preferred examples, one or more ascorbate compounds such as ascorbic acid are present in a pharmaceutical composition in an amount of 5 mg/mL or greater.

In certain preferred examples, one or more ascorbate compounds such as ascorbic acid are present in a pharmaceutical composition in an amount of 6 mg/mL or greater.

In certain preferred examples, one or more ascorbate compounds such as ascorbic acid are present in a pharmaceutical composition in an amount of 7 mg/mL or greater.

In certain preferred examples, one or more ascorbate compounds such as ascorbic acid are present in a pharmaceutical composition in an amount of 8 mg/mL or greater.

In certain preferred examples, one or more ascorbate compounds such as ascorbic acid are present in a pharmaceutical composition in an amount of 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg/mL or greater.

In certain preferred examples, one or more ascorbate compounds such as ascorbic acid are present in a pharmaceutical composition in an amount of not exceeding 20, 19, 18, 17, 16, 15, 14, 13, 12, 11 or 10 mg/mL.

In certain preferred examples, one or more ascorbate compounds such as ascorbic acid are present in a pharmaceutical composition in an amount of not exceeding 20, 19, 18, 17, 16, 15, 14, 13, 12, 11 or 10 mg/mL.

In certain preferred examples, one or more ascorbate compounds such as ascorbic acid are present in a pharmaceutical composition in an amount of between 2 and 10 mg/mL.

In certain preferred examples, one or more ascorbate compounds such as ascorbic acid are present in a pharmaceutical composition in an amount of between 2 and 5 mg/mL.

In certain preferred examples, one or more ascorbate compounds such as ascorbic acid are present in a pharmaceutical composition in an amount of between 3 and 5 mg/mL.

In certain preferred examples, one or more ascorbate compounds such as ascorbic acid are present in a pharmaceutical composition in an amount of between 3 and 4 mg/mL.

In certain preferred examples, one or more ascorbate compounds such as ascorbic acid are present in a pharmaceutical composition in an amount of 3.3 mg/mL, 3.4 mg/mL. 3.5 mg/mL, 3.6 mg/mL, 3.7 mg/mL or 3.8 mg/mL.

In certain examples, a pharmaceutical composition will contain a single ascorbate compound. In certain additional preferred examples, a pharmaceutical composition will contain a single ascorbate compound that is ascorbic acid.

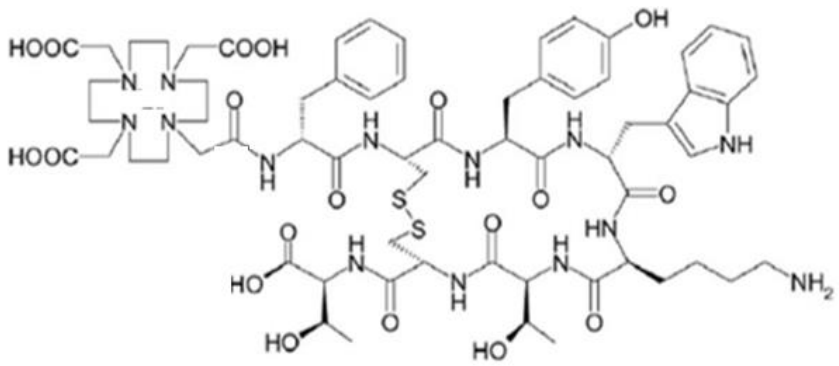
It has been found that a substantial or complete absence of one or more gentisate compounds during the incorporation reaction can reduce or avoid the occurrence or formation of an impurity that has been detected by high-performance liquid chromatography (HPLC).

In certain examples, pharmaceutical composition will be substantially or completely free of a gentisate adduct impurity. An impurity or impurities observed upon use of one or more gentisate compounds such as gentisic acid for example during the incorporation reaction to form a complex of lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE) or otherwise may be present in an incorporation reaction admixture or pharmaceutical composition is sometimes referred to herein as “gentisate adduct impurity”. A gentisate adduct impurity can be assessed by HPLC. A pharmaceutical composition will be substantially free of a gentisate adduct impurity if an HPLC analysis shows minimal or no observation (naked eye observation of HPLC chromatograph) of the gentisate adduct impurity. A pharmaceutical composition will be completely free of a gentisate adduct impurity if an HPLC analysis shows no observation (naked eye observation of HPLC chromatograph) of the gentisate adduct impurity.

Suitably, the pharmaceutical composition is an aqueous formulation. In certain preferred examples, a pharmaceutical composition does not contain an alcohol such as ethanol or other organic solvent. In certain preferred examples, a pharmaceutical composition is at least substantially free (i.e. less than 5, 4, 3, 2, 1 or 0.5 weight percent based on total composition weight) of an alcohol such as ethanol or other organic solvent.

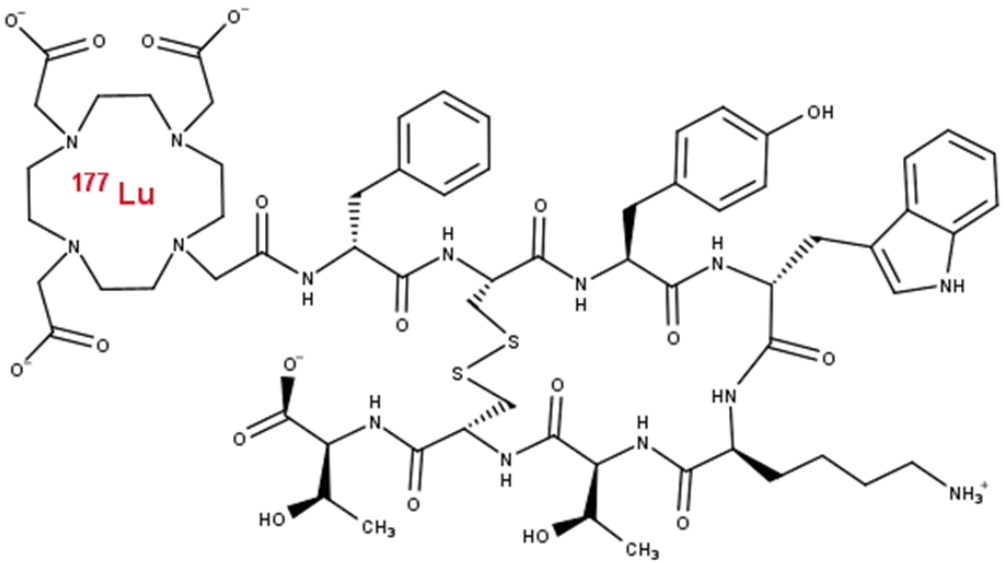
In certain preferred examples, a pharmaceutical composition has a pH of 4.0 to 6.5. In additional preferred example, pharmaceutical composition has a pH of 4.5 to 6.0.

The compound tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE) has the following structure 1:



1

^{177}Lu-DOTATATE is a lutetium-177 complex of the above compound 1 and may be represented by the following structure 2:



2

In an example, methods are provided for preparing ^{177}Lu-DOTATATE (structure 2 above), which includes admixing lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE, structure 1 above) in the presence of one or more ascorbate compounds and forming a complex of ^{177}Lu and DOTATATE. This reaction to form a complex of ^{177}Lu and DOTATATE (e.g. such complex including structure 2 above) that may include admixing ^{177}Lu and DOTATATE is sometimes referred to herein as an "incorporation reaction".

The one or more ascorbate compounds are suitably present in an incorporation reaction and/or a pharmaceutical composition in an amount of 20 g/mL or less, including 18, 16, 14, 12, 0, 9, 8, 7, 6, 5, 4, 3 or 2 mg/mL or less.

In preferred examples, the tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE) is admixed with lutetium-177 as an aqueous formulation in the incorporation reaction mixture.

In certain examples, in an incorporation reaction and/or a pharmaceutical composition, the one or more ascorbate compounds include ascorbic acid. In certain examples, in an incorporation reaction and/or a pharmaceutical composition, the one or more ascorbate compounds include an ascorbate salt such as sodium ascorbate.

Preferably, prior to the incorporation reaction or addition to ^{177}Lu-DOTATATE to provide a pharmaceutical composition, the ascorbate compound such as sodium ascorbate or ascorbic acid is assessed for purity or absence of a material that may inhibit the incorporation reaction of lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE). For instance, a sample from a lot of an ascorbate compound such as an ascorbate metal salt e.g. sodium ascorbate can be tested such as in a test-scale (small-scale) incorporation reaction of lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE) to ensure the ascorbate compound lot does not adversely impact the formation of the complex of lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE) or the radiochemical stability of the formed complex over time.

Accordingly, methods are provided that comprise determining purity of an ascorbate compound prior to admixing the ascorbate compound with lutetium-177 and/or tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE) and/or a complex of lutetium-177 and/or tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE). Suitably, the ascorbate compound is determined to be effective in an incorporation reaction and method comprises admixing the effective ascorbate compound with lutetium-177 and/or tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE) and/or a complex of lutetium-177 and/or tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE). In such methods, the ascorbate compound may be ascorbic acid or an ascorbate salt, such as sodium ascorbate.

In certain preferred examples, the admixture of lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE) is heated. In particular examples, the admixture is heated for 60 minutes or less, for 50 minutes or less, for 40 minutes, for 30 minutes or less, for 20 minutes or less, or for 15 minutes or less.

In certain preferred examples, the admixture of lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE) is heated at about 80^{o}C $\pm$ 10^{o}C, or at about 80^{o}C $\pm$ 5^{o}C.

In certain preferred examples, the present methods include cooling the admixture following heating.

In certain preferred examples, following the admixing, the complex of lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE) is mixed with a formulation composition. Preferably, the formulation composition is an aqueous composition that includes one or more stabilizer compounds, particularly one or more ascorbate compounds, such ascorbic acid. The formulation composition suitably includes one or more additional stabilizer compounds present in an amount of 1, 2, 3 5, 6, 7, 8, 9, 100, 11, 12, 13, 14, 15 or 20 mg/mL or greater. As discussed above, the formulation composition is preferably at least substantially or completely free of a gentisate compound such as gentisic acid.

In certain preferred examples, a formulation composition further comprises one or more sequestering agents.

In certain preferred examples, incorporation of lutetium-177 into or with tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE) to provide ^{177}Lu-DOTATATE is preferably greater than 98 mole percent, or greater than 99 mole percent based on the molar equivalent of lutetium-177 used in the incorporation reaction.

In certain preferred examples, an acidic aqueous formulation of lutetium-177 is admixed with the tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE). Preferably, a hydrogen halide or acid halide aqueous formulation of lutetium-177 is admixed with the tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE). For example, a hydrochloride acid aqueous formulation of lutetium-177 is admixed with the tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE).

In an example, provided is ^{177}Lu-DOTATATE obtainable, or obtained by the methods described herein.

In an example, provided is a pharmaceutical composition including ^{177}Lu-DOTATATE as described herein. Preferably, radiochemical purity of the composition is 95% or greater for 3 days or more at 25 ^{o}C, or 95% or greater for 4 days or more at 25 ^{o}C, or 95% or greater for 5 days or more at 25 ^{o}C. As referred to herein, radiochemical purity is preferably assessed via HPLC analysis, particularly HPLC radiometric detection (i.e. radio-HPLC).

In an example, provided is a single dosage kit including ^{177}Lu-DOTATATE or pharmaceutical composition described herein. Moreover, provided is a multiple dosage kit including the ^{177}Lu-DOTATATE or pharmaceutical composition described herein.

In an example, provided is a method of treating a subject suffering from cancer. The method includes administering to the subject an effective amount of ^{177}Lu-DOTATATE or pharmaceutical composition described herein.

In certain examples, the subject is suffering from a neuroendocrine tumor. In certain examples, the subject is suffering from neuroendocrine tumors that originate from foregut, hindgut, midgut, lung, ovary, medulla, adrenal medulla, adrenal, kidney, pituitary, thyroid or paraganglia.

In certain examples, the subject is suffering from a gastroenteropancreatic neuroendocrine tumor (GEP-NET), foregut, midgut and hindgut neuroendocrine tumors.

In certain examples, the subject is suffering from unresectable or metastatic neuroendocrine tumor(s).

In certain examples, the methods include identifying a patient for treatment by assessing neuroendocrine tumors of the patient to be somatostatin receptor positive, for example with ^{68}Ga-DOTATATE and a positron emission tomography scan.

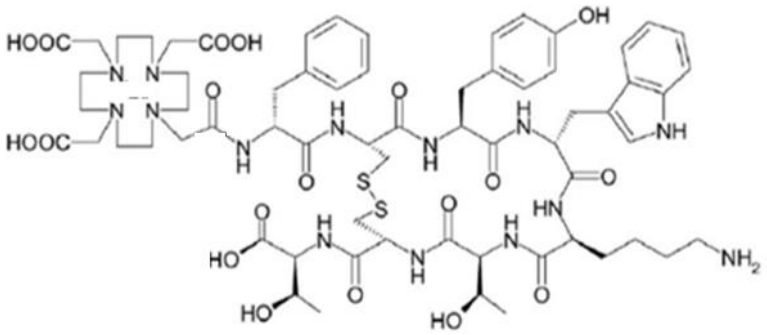
Use of the ^{177}Lu-DOTATATE compound and compositions to treat a disease or disorder as disclosed herein is also provided.

Further provided are methods for manufacture of a medicament that comprises the ^{177}Lu-DOTATATE compound and composition to treat a disease or disorder as disclosed herein.

Other examples of the present disclosure are disclosed *infra*.

Detailed Description of the Invention

As discussed above, ^{177}Lu-DOTATATE is a lutetium-177 ($^{177}Lu^{3+}$) complex of the compound 1



1

and may be represented by the following structure 2:

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising:

(a) a complex of lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE); and

(b) one or more ascorbate compounds, wherein the composition is substantially or completely free of stabilizer compounds other than the one or more ascorbate compounds.

2. The pharmaceutical composition of claim 1 wherein the one or more ascorbate compounds are present in the composition in an amount of 10 mg/mL or less.

3. The pharmaceutical composition of claim 1 or 2 wherein the one or more ascorbate compounds are present in the composition in an amount of between 2.5 and 4.5 mg/mL.

4. The pharmaceutical composition of any one of claims 1 through 3 wherein the complex of lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE) is present in an amount of at least 5 mCi/mL.

5. The pharmaceutical composition of any one of claims 1 through 4 wherein the radiochemical purity of the composition is 95% or greater for 3 days by HPLC analysis.

6. The pharmaceutical composition of any one of claims 1 through 5 wherein the radiochemical purity of the composition is 95% or greater for 3 days or more at 25^{o}C.

7. The pharmaceutical composition of any one of claims 1 through 6 wherein the composition as a pH of 4.0 to 6.0.

8. A method for preparing the pharmaceutical composition of any one of claims 1 through 7, comprising the steps of:

a) admixing lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE) in aqueous solution in the presence of one or more ascorbate compounds in a

concentration of 40 mg/mL or less, in the substantial or complete absence of a second stabilizing agent, and

b) heating the admixture, thereby forming an aqueous solution comprising a complex of lutetium-177 and tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE);

c) mixing the aqueous solution of step b) with an aqueous formulation composition comprising one or more ascorbate compounds in the substantial or complete absence of a second stabilizing agent.

9. The method of claim 8 wherein the admixture is heated for 60 minutes or less.

10. The method of any one of claims 8 through 9 wherein the admixture is heated at about $80^{o}C \pm 10^{o}C$.

11. The method of any one of claims 8 through 10 wherein the formulation composition comprises the one or more ascorbate compounds in an amount of 1 mg/mL or greater.

12. The method of any one of claims 8 through 11 wherein the formulation composition further comprises one or more sequestering agents.

13. The method of any one of claims 8 through 12 wherein the reaction of lutetium-177 with tetraazacyclododecane tetra-acetic acid-octreotate (DOTATATE) provides ^{177}Lu-DOTATATE in greater than 98 mole percent.

14. Use of a pharmaceutical composition of any one of claims 1 through 7 in the manufacture of a medicament for treating cancer in a subject in need thereof.

15. The use of claim 14 wherein the one or more ascorbate compounds are present in the pharmaceutical composition in an amount of 10 mg/mL or less.

16. The use of any one of claims 14 through 15 wherein the one or more ascorbate compounds are present in the pharmaceutical composition in an amount of 6 mg/mL or less.

17. The use of any one of claims 14 through 16 wherein the subject is suffering from a neuroendocrine tumor.

18. The use of any one of claims 14 through 17 wherein the neuroendocrine tumor originates from foregut, hindgut, midgut, lung, ovary, medulla, adrenal medulla, adrenal, kidney, pituitary, thyroid or paraganglia.

19. A single dosage kit comprising the pharmaceutical composition of any one of claims 1 through 7.

20. A multiple dosage kit comprising the pharmaceutical composition of any one of claims 1 through 7.

21. A sealed container comprising the pharmaceutical composition of any one of claims 1 through 7.

22. The pharmaceutical composition of any one of claims 1 through 7 for use in therapy.