Polymorphic Forms of ST-246 and Methods of Preparation

~~CROSS REFERENCE TO RELATED APPLICATIONS~~

[00001] ~~This application claims priority to and benefit of U.S. Provisional Application No. 61/316,747, filed March 23, 2010 and U.S. Provisional Application No. 61/373,031, filed August 12, 2010, the contents of which are hereby incorporated by reference in their entirety.~~

FIELD OF THE INVENTION

[00002] The present invention relates to particular crystalline forms of a pharmaceutical compound, 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide, named ST-246, to processes for their preparation, pharmaceutical composition comprising different crystalline forms and its use in therapy..

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[00003] This invention was made with U.S. government support under Contract No. HHSN266200600014C awarded by the National Institutes of Health (NIH). The US government has certain rights in this invention.

BACKGROUND OF THE INVENTION

[00004] Throughout this application, various publications are referenced within the text. ~~The disclosure of these~~

~~publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art as known to those skilled in therein as of the date of the invention described and claimed herein.~~

[00005] Following the eradication of smallpox (Fenner et al., The epidemiology of smallpox. In: Smallpox and its eradication. Switzerland: World Health Organization; 1988) and the subsequent cessation of routine childhood vaccinations for smallpox, the number of people susceptible to infection with variola virus (VARV), the etiologic agent that causes smallpox, has dramatically increased worldwide. In addition, encroachment into wildlife habitats, the trade of exotic pets, and the trade of bush meat increase the risk for zoonotic infection with other orthopoxviruses, such as monkeypox virus (MPXV), for which vaccination against smallpox provides some cross protection (Jezek et al., Human monkey pox. In: Melnick JL ed. Monographs in virology. Vol. 17. Basel, Switzerland: S Karger AG. 1988:81-102).

[00006] Given that a large proportion of the worldwide population is susceptible to smallpox, the emergence of MPXV in the United States in 2003, and the continued concern over the intentional release of VARV, there is renewed interest in the development of safer smallpox and other orthopoxvirus vaccines and antiviral therapeutics.

[00007] One recently discovered antiviral compound is ST-246, a specific and potent inhibitor of an orthopoxvirus protein critical for virus maturation. Several studies evaluating ST-246 for activity against orthopoxviruses have demonstrated excellent in vitro and in vivo efficacy (Quenelle et al. 2007. Efficacy of delayed treatment with ST-246 given orally against

CLAIMS:

1. A polymorph Form I of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) which shows an X-ray powder diffraction pattern having characteristic peaks at a reflection angle 2θ of about 7.63, 10.04, 11.47, 14.73, 15.21, 15.47, 16.06, 16.67, 16.98, 18.93, 19.96, 20.52, 20.79, 22.80, 25.16, 26.53, 27.20, 27.60, 29.60, 30.23, 30.49, 30.68, 31.14, 33.65, 34.33, 35.29, 35.56, 36.30, 37.36, 38.42, 38.66 degrees.

2. An isolated polymorph according to claim 1 that is at least 70% free of other forms.

3. An isolated polymorph according to claim 2~~, especially~~ that is at least 80% free of other forms.

4. An isolated polymorph according to claim 3~~, more especially~~ that is at least 90% free of other forms.

5. An isolated polymorph according to claim 4~~, even more especially~~ that is at least 95% free of other forms.

6. An isolated polymorph according to claim 5~~, for example~~ that is at least 99% free of other forms.

~~3~~7. A pharmaceutical composition~~, for example formulated for oral administration,~~ comprising the polymorph of claim 1 and further comprising one or more pharmaceutically acceptable ingredients selected from the group consisting of carriers, excipients, diluents, additives, fillers, lubricants and binders.

8. The pharmaceutical composition of claim 7 formulated for oral administration.

~~4~~9. A composition comprising a therapeutically effective amount of the polymorph of claim 1, for use in treating Orthopoxvirus infections or eczema vaccinatum.

~~5. A polymorph Form II of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) which shows a X-ray powder diffraction pattern having characteristic peaks at a reflection angle 2θ according to Figure 2.~~

~~6. An isolated polymorph according to claim 5 that is at least 70% free of other forms, especially that is at least 80%% free of other forms, more especially that is at least 90% % free of other forms, still more especially that is at least 95% % free of other forms, for example that is at least 99% free of other forms.~~

~~7. A pharmaceutical composition, for example formulated for oral administration, comprising the polymorph of claim 5 and further comprising one or more pharmaceutically acceptable ingredients selected from the group consisting of carriers, excipients, diluents, additives, fillers, lubricants and binders.~~

~~8. A composition comprising a therapeutically effective amount of the polymorph of claim 5 for use in treating Orthopoxvirus infections or eczema vaccinatum.~~

~~9. A polymorph Form III of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) which shows an X-ray powder diffraction pattern having characteristic peaks at a reflection angle 2θ of about 6.71, 9.05, 12.49, 13.03, 13.79, 14.87, 15.72, 16.26, 16.74, 18.10, 18.43, 19.94, 21.04, 21.51, 23.15, 23.51, 25.32, 26.24, 26.87,~~

~~27.32, 27.72, 28.55, 29.08, 29.50, 29.84, 31.27, 33.48, 35.36, 39.56 degrees.~~

~~10. An isolated polymorph according to claim 9 that is at least 70% free of other forms, especially that is at least 80% free of other forms, more especially that is at least 90% free of other forms, still more especially that is at least 95% pure free of other forms, for example that is at least 99% free of other forms.~~

~~11. A pharmaceutical composition, for example formulated for oral administration, comprising the polymorph of claim 9 and further comprising one or more pharmaceutically acceptable ingredients selected from the group consisting of carriers, excipients, diluents, additives, fillers, lubricants and binders.~~

~~12. A composition comprising a therapeutically effective amount of the polymorph of claim 9 for use in treating Orthopoxvirus infections or eczema vaccinatum.~~

~~13. A polymorph Form IV of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) which shows an X-ray powder diffraction pattern having characteristic peaks at a reflection angle 2θ as shown in Figure 4.~~

~~14. An isolated polymorph according to claim 13 that is at least 70% free of other forms, especially that is at least 80% free of other forms, more especially that is at least 90% free of other forms, still more especially that is at least 99% free of other forms, for example that is at least 99.9% free of other forms.~~

~~15. A pharmaceutical composition, for example formulated for oral administration, comprising the polymorph of claim 13 and~~

~~further comprising one or more pharmaceutically acceptable ingredients selected from the group consisting of carriers, excipients, diluents, additives, fillers, lubricants and binders.~~

~~16. A composition comprising a therapeutically effective amount of the polymorph of claim 13 for use in treating Orthopoxvirus infections or eczema vaccinatum.~~

~~17. A polymorph Form VI of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) which shows an X-ray powder diffraction pattern having characteristic peaks at a reflection angle 2θ as shown in Figure 6.~~

~~18. An isolated polymorph according to claim 17 that is at least 70% free of other forms, especially that is at least 80% free of other forms, more especially that is at least about 90% free of other forms, still more especially that is at least 95% free of other forms, for example that is at least 99% free of other forms.~~

~~19. A pharmaceutical composition, for example formulated for oral administration, comprising the polymorph of claim 17 and further comprising one or more pharmaceutically acceptable ingredients selected from the group consisting of carriers, excipients, diluents, additives, fillers, lubricants and binders.~~

~~20. A composition comprising a therapeutically effective amount of the polymorph of claim 17 for treating Orthopoxvirus infections or eczema vaccinatum.~~

~~21~~10. A method of producing a crystal polymorphic Form I of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-

dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246), comprising the steps of:

a) dissolving 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) in at least one organic solvent and an amount of water to make a solution;

b) cooling said solution to a temperature that causes the preferential crystallization of said 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) polymorphic Form I; and

c) optionally drying the formed crystals of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246),

wherein said organic solvent is selected from a group consisting of isopropyl alcohol (IPA), ethyl acetate, ethanol, methanol, acetone, isopropyl acetate and tetrahydrofuran (THF).

~~22~~11. The method of claim ~~21~~ 10 further comprising adding seed crystals of polymorphic Form I of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) during step (b).

~~23~~12. The method of claim ~~21~~10, wherein said organic solvent is methanol, THF, ethyl acetate or isopropyl alcohol.

~~24~~13. The method of claim ~~21~~10, wherein said cooling step takes place over at least 15 minutes.

14. The method of claim 13, wherein said cooling step takes place ~~, such as~~ over at least 2 hours.

15. The method of claim 14, wherein said cooling step takes place~~, for example~~ over at least 5 hours.

~~25~~16. The method of claim ~~21~~10, wherein the organic solvent is ethyl acetate and the water content is about 40% by volume of total solvent volume, wherein the organic solvent is ethyl acetate and the water content is about 5% by volume of total solvent volume, wherein the organic solvent is ethyl acetate and the water content is about 3% by volume of total solvent volume, wherein the organic solvent is ethyl acetate and the water content is about 2% by volume of total solvent volume, or wherein the organic solvent is isopropyl alcohol and the water content is about 5% by volume of total solvent volume.

~~26. A method of producing crystal polymorphic Form II of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246), comprising the steps of:~~

~~a) dissolving 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) in at least one solvent to make a solution;~~

~~b) cooling said solution to a temperature that causes the preferential crystallization of said 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) polymorphic Form II; and~~

~~c) optionally drying the formed crystals of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246),~~

~~wherein said solvent is selected from the group consisting of ethyl acetate, chloroform and 1-propanol, isopropyl alcohol (IPA), ethanol, acetone, acetonitrile (ACN), toluene, isopropyl acetate and dimethylformamide (DMF) or wherein 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) is dissolved in ethanol and water.~~

~~27. The method of claim 26 further comprising adding seed crystals of polymorphic Form II 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) during step (b).~~

~~28. The method of claim 26, wherein said solvent does not contain water.~~

~~29. The method of claim 26, wherein said solvent is selected from the group consisting of ethyl acetate and chloroform.~~

~~30. The method of claim 26, in which 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) is dissolved in ethanol and water wherein the volume ratio of ethanol: water is about 1:1.~~

~~31. A method of producing crystal polymorphic Form III of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246), comprising the steps of:~~

~~a) dissolving 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) in water and at least one organic solvent selected from the group consisting of isopropyl alcohol (IPA), ethyl acetate and ethanol, or in at least one organic solvent selected from the group consisting of acetone, isopropyl alcohol (IPA), dimethylformamide (DMF), dimethylamine (DMA), pyridine, trifluoroethanol (TFE), methanol, ethanol, chloroform, acetonitrile (ACN), and tetrahydrofuran (THF) to make a solution;~~

~~b) cooling said solution to a temperature that causes the preferential crystallization of said 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-~~

~~ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) polymorphic Form III; and~~

~~c) optionally drying the formed crystals of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246).~~

~~32. The method of claim 31 further comprising adding seed crystals of polymorphic Form III of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) during step (b).~~

~~33. The method of claim 31, in which 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) is dissolved in water and at least one organic solvent selected from the group consisting of isopropyl alcohol (IPA), ethyl acetate and ethanol, wherein said cooling step takes place over less than 15 minutes.~~

~~34. A method for producing crystal polymorphic Form III of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246), comprising the steps of:~~

~~a) suspending an anhydrous form of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) or polymorphic Form V in water; and~~

~~b) optionally drying the formed crystals of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246).~~

~~35. A method of producing crystal polymorphic Form IV of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-~~

4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246), comprising the steps of:

a) dissolving 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) in at least one organic solvent optionally containing water to make a solution, wherein said solvent is selected from the group consisting of: a mixture of acetonitrile and ethyl acetate, a mixture of ethanol and toluene, a mixture of water and ethyl acetate, and a mixture of trifluoroethanol and THF, or dissolving 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) in at least one solvent to make a solution wherein said solvent is selected from the group consisting of 1-butanol, trifluoroethanol (TFE), chloroform, dichloromethane and toluene, especially 1-butanol;

b) cooling said solution to a temperature that causes the preferential crystallization of said 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) polymorphic Form IV: and

c) optionally drying the formed crystals of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246).

36. The method of claim 35 further comprising adding seed crystals of polymorphic Form IV of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) during step (b).

37. The method of claim 35, wherein said solvent is a mixture of acetonitrile and ethyl acetate at a volume ratio of about 1:4, a mixture of ethanol and toluene at a volume ratio of about 1:4, a mixture of water and ethyl acetate at a volume

~~ratio of about 1:4, and a mixture of trifluoroethanol and THF at a volume ratio of about 1:1.~~

~~38. The method of claim 35, in which said solvent is selected from the group consisting of 1-butanol, trifluoroethanol (TFE), chloroform, dichloromethane and toluene wherein said solvent does not contain water.~~

~~39. A method of producing crystal polymorphic Form VI of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246), comprising the steps of:~~

~~a) dissolving 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) in at least one solvent to make a solution;~~

~~b) cooling said solution to a temperature that causes the preferential crystallization of said 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) polymorphic Form VI; and~~

~~c) optionally drying the formed crystals of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246),~~

~~wherein said solvent is selected from the group consisting of nitromethane, methanol and chloroform, especially nitromethane.~~

~~40. The method of claim 39 further comprising adding seed crystals of polymorphic Form VI of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) during step (b).~~

~~41. The method of claim 39, wherein said solvent does not contain water.~~

~~42. A dosage unit form in the form of a capsule or a tablet comprising the pharmaceutical composition of claim 3-7 which is formulated for oral administration, wherein 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) has a D90% particle size diameter of up to about 300 microns.~~

~~43. A dosage unit form comprising the pharmaceutical composition of claim 3-7 which is formulated for oral administration, comprising 200 mg of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) wherein a D90% particle size is less than about 10 microns.~~

~~44~~19. A dosage unit form for oral administration comprising the pharmaceutical composition of claim ~~3~~7, ~~7, 11, 15 or 19,~~ wherein 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) has a D90% particle size diameter of up to about 300 microns.

~~20~~18. The dosage unit form for oral administration of claim ~~1~~7, ~~for example,~~ wherein 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) has a D90% particle size diameter of about 5 microns~~,~~.

~~21~~19. The dosage unit form for oral administration of claim ~~1~~7, wherein 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) has a D90% particle size diameter of about 16.6 microns.

~~22~~20. The dosage unit form for oral administration of claim ~~1~~7, wherein 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-

benzamide (ST-246) has~~,~~ a D90% particle size diameter of about 26.6 microns.

~~23~~21. ~~or~~ The dosage unit form for oral administration of claim ~~19~~17, wherein 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) has a D90% particle size diameter of about 75 microns.

~~45~~2422. A unit dosage form for oral administration comprising:

(a) about 200 mg of 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246), wherein said 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) is present as ~~selected from the group consisting of~~ polymorph Form I~~, polymorph Form II, polymorph Form III, polymorph Form IV and polymorph Form VI~~;

(b) about 33.15 mg of lactose monohydrate;

(c) about 42.90 mg of croscarmellose sodium;

(d) about 1.95 mg of colloidal silicon dioxide;

(e) about 13.65 mg of hydroxypropoyl methylcellulose;

(f) about 7.8 mg of sodium lauryl sulfate;

(g) about 1.95 mg of magnesium stearate; and

(h) a quantity of microcrystalline cellulose up to about 88.60 mg such that the total weight of the dosage form is about 390 mg.

~~46. A unit dosage according to claim 45, wherein said 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide (ST-246) is present as polymorph Form I.~~