CLAIMS

We claim:

1. A pharmaceutical composition comprising an effective amount of at least one active compound selected from at least methylnaltrexone or a pharmaceutically acceptable salt thereof, a calcium salt, and a chelating agent in an aqueous solution.

2. The pharmaceutical composition of claim 1, wherein the calcium salt and chelating agent are provided together as a calcium salt chelating agent.

3. The pharmaceutical composition of claim 2 wherein the calcium salt chelating agent is selected from the group calcium ethylenediaminetetraacetic acid (EDTA), calcium diethylenetriaminepentaacetic acid (DTPA), calcium hydroxyethylenediaminetriacetic acid (HEDTA), calcium ethylene glycol-bis-(2-aminoethyl)-N,N,N', N'-tetraacetic acid (EGTA), calcium nitrilotriacetic acid (NTA), calcium citrate, and calcium salt derivatives thereof.

4. The pharmaceutical composition of claim 1 wherein the active compound is methylnaltrexone bromide.

5. The pharmaceutical composition of claim 1, further comprising an isotonic agent.

6. The pharmaceutical composition of claim 5 wherein the isotonic agent is selected from the group consisting of sodium chloride, mannitol, lactose, dextrose, glycerol, and sorbitol.

7. The pharmaceutical composition of claim 5, wherein the isotonic agent comprises a delivery vehicle selected from the group consisting of 5% Dextrose, Lactated Ringer's Injection, 0.45% NaCl, 0.65% NaCl, and 0.9% NaCl.

8. The pharmaceutical composition of claim 3, wherein the calcium salt chelating agent is calcium ethylenediaminetriacetic acid (EDTA),or calcium ethylene glycol-bis-(2-aminoethyl)-N,N,N', N'-tetraacetic acid (EGTA), or calcium salt derivatives thereof.

9. The pharmaceutical composition of claim 1, wherein the solution has a pH of between 2.5 and pH 6.

10. The pharmaceutical composition of claim 9, wherein the pH is between about pH 3 and about pH 4.

11. The pharmaceutical composition of claim 1, further comprising a stabilizing agent selected from the group consisting of glycine, benzoic acid, citric, glycolic, lactic, malic, and maleic acid

12. A pharmaceutical composition comprising an effective amount of at least one active compound selected from at least methylnaltrexone or a pharmaceutically acceptable salt thereof, a calcium salt chelating agent, and a stabilizing agent in an aqueous solution, wherein the solution has a pH of between 2.5 and 6.0.

13. The pharmaceutical composition of claim 12, wherein the calcium salt chelating agent is selected from the group calcium ethylenediaminetetraacetic acid (EDTA), calcium diethylenetriaminepentaacetic acid (DTPA), calcium hydroxyethylenediaminetriacetic acid (HEDTA), calcium ethylene glycol-bis-(2-aminoethyl)-N,N,N', N'-tetraacetic acid (EGTA), calcium nitrilotriacetic acid (NTA), calcium citrate, and calcium salt derivatives thereof.

14. The pharmaceutical composition of claim 12 wherein the active compound is methylnaltrexone bromide.

15. The pharmaceutical composition of claim 12, further comprising an isotonic agent.

16. The pharmaceutical composition of claim 15 wherein the isotonic agent is selected from the group consisting of sodium chloride, mannitol, lactose, dextrose, glycerol, and sorbitol.

17. The pharmaceutical composition of claim 16, wherein the isotonic agent comprises a delivery vehicle selected from the group consisting of 5% Dextrose, Lactated Ringer's Injection and 0.65%NaCl and 0.9% NaCl.

18. The pharmaceutical composition of claim 12, wherein the aqueous solution comprises water for injection.

19. The pharmaceutical composition of claim 13, wherein the calcium salt chelating agent is calcium ethylenediaminetriacetic acid (EDTA)or calcium ethylene glycol-bis-(2-aminoethyl)-N,N,N', N'-tetraacetic acid (EGTA), or calcium salt derivatives thereof.

20. The pharmaceutical composition according to claim 12 wherein the stabilizing agent is glycine.

21. The pharmaceutical composition according to claim 20 wherein the glycine is glycine-HCl.

22. The pharmaceutical composition according to claim 12, wherein an effective amount of glycine maintains the pH at about 3.0 to about 4.0.

23. The pharmaceutical composition according to claim 22 wherein the pH is about 3.5.

24. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is a unit dose contained in a vial, ampoule, or syringe for subcutaneous administration to a subject.

25. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is a dose concentrate for use as addition to an intravenous container, an intravenous bag or intravenous bottle for intravenous administration to a subject.

26. The pharmaceutical composition to claim 1, wherein the pharmaceutical composition is a dose concentrate in a sealed container wherein the container has a space sufficient for introduction of a volume of aqueous solvent sufficient to form a diluted solution of the dose concentrate.

27. The pharmaceutical composition according to claim 12, wherein the pharmaceutical composition is a unit dose contained in a vial, ampoule, or syringe for subcutaneous administration.

28. The pharmaceutical composition according to claim 12, wherein the pharmaceutical composition is a dose concentrate for use as addition to an intravenous container, an intravenous bag or intravenous bottle for intravenous administration.

29. The pharmaceutical composition to claim 12, wherein the pharmaceutical composition is a dose concentrate in a sealed container wherein the container has a space sufficient for introduction of a volume of aqueous solvent sufficient to form a diluted solution of the dose concentrate.

30. A pharmaceutical composition comprising methylnaltrexone or a pharmaceutically acceptable salt thereof, calcium EDTA or a calcium salt derivative thereof, and glycine in an aqueous carrier.

31. The pharmaceutical composition of claim 30, characterized by one or more of (a) through (d):

a. the methylnaltrexone is methylnaltrexone bromide;
b. the calcium EDTA is calcium EDTA disodium;
c. the glycine is glycine hydrochloride; and

d. the aqueous carrier is isotonic sodium chloride.

32. The pharmaceutical composition of claim 31, wherein the composition has a pH of between about pH 3 and about pH 4.

33. The pharmaceutical composition of claim 32, characterized by each of (a) through (d).

34. The pharmaceutical composition of claim 33, wherein the composition has a pH between about pH 3.4 and about pH 3.6.

35. A pharmaceutical composition comprising an effective amount of methylnaltrexone, or a pharmaceutically acceptable salt thereof, a calcium salt chelating agent, and a stabilizing agent in an aqueous solution, wherein a concentration of degradation products in the composition following six months of room temperature storage conditions is characterized by one or more of the following characteristics (a) through (g):

a. the total degradation products does not exceed about 1.25% of methylnaltrexone;

b. the concentration 2,2' bis-methylnaltrexone degradant product (RRT 1.55) does not exceed about 0.2% of methylnaltrexone;

c. the concentration 7-dihydroxymethylnaltrexone degradant product (RRT 0.67) does not exceed about 0.2% of methylnaltrexone;

d. the concentration the ring contracted methylnaltrexone degradant product (RRT 0.79) does not exceed about 0.2% of methylnaltrexone;

e. the aldol dimer methylnaltrexone degradant product (RRT 1.77) does not exceed about 0.2% of methylnaltrexone;

f. the Hoffman elimination methylnaltrexone degradant product (RRT 2.26) does not exceed about 0.2% of methylnaltrexone; and

g. the concentration of O-methyl methylnaltrexone (RRT 1.66) does not exceed about 0.25% of methylnaltrexone.

36. The pharmaceutical composition of claim 35, characterized by each of (a) through (g).

37. A pharmaceutical composition comprising an effective amount of methylnaltrexone or a pharmaceutically acceptable salt thereof, a calcium salt chelating agent, and a stabilizing agent in an aqueous solution, wherein a concentration of degradation products in the composition following six months of room temperature storage conditions is characterized by one or more of the following characteristics (a) through (g):

a. the concentration of total degradation products does not exceed about 0.75% of methylnaltrexone;

b. the concentration 2,2' bis-methylnaltrexone degradant product (RRT 1.55) does not exceed about 0.1% of methylnaltrexone;

c. the concentration 7-dihydroxymethylnaltrexone degradant product (RRT 0.67) does not exceed about 0.1% of methylnaltrexone;

d. the concentration the ring contracted methylnaltrexone degradant product (RRT 0.79) does not exceed about 0.15% of methylnaltrexone;

e. the aldol dimer methylnaltrexone degradant product (RRT 1.77) does not exceed about 0.05% of methylnaltrexone;

f. the Hoffman elimination methylnaltrexone degradant product (RRT 2.26) does not exceed about 0.1% of methylnaltrexone; and

g. the concentration of O-methyl methylnaltrexone (RRT 1.66) does not exceed about 0.15% of methylnaltrexone.

38. The pharmaceutical composition of claim 37, characterized by each of (a) through (g).

39. A method of preparing a methylnaltrexone formulation for parenteral administration, the method comprising the steps of:

preparing a solution comprising methylnaltrexone or a pharmaceutically acceptable salt thereof, an isotonic agent and a calcium salt chelating agent; and

sterilizing the resulting solution and distributing to one or more sealed containers.

40. The method of claim 39, wherein the calcium salt chelating agent is selected from the group calcium ethylenediaminetetraacetic acid (EDTA), calcium diethylenetriaminepentaacetic acid (DTPA), calcium hydroxyethylenediaminetriacetic acid (HEDTA), calcium ethylene glycol-

bis-(2-aminoethyl)-N,N,N', N'-tetraacetic acid (EGTA), calcium nitrilotriacetic acid (NTA), calcium citrate, and calcium salt derivatives thereof.

41. The method of claim 39 wherein the active compound is methylnaltrexone bromide.

42. The method of claim 39, wherein the solution comprises an isotonic agent.

43. The method of claim 42 wherein the isotonic agent is selected from the group consisting of sodium chloride, mannitol, lactose, dextrose, glycerol, and sorbitol.

44. The method of claim 43, wherein the isotonic agent comprises a delivery vehicle selected from the group consisting of 5% Dextrose, Lactated Ringer's Injection and 0.65%NaCl and 0.9% NaCl.

45. The method of claim 39, wherein the solution comprises water for injection.

46. The method of claim 39, wherein the calcium salt chelating agent is calcium ethylenediaminetriacetic acid (EDTA) or calcium ethylene glycol-bis-(2-aminoethyl)-N,N,N', N'-tetraacetic acid (EGTA) or a calcium salt derivative thereof.

47. The method of claim 39 wherein the solution comprises a stabilizing agent.

48. The method of claim 47, wherein the stabilizing agent is glycine.

49. The method of claim 48, wherein an effective amount of glycine maintains pH at about 3.0 to about 4.0.

50. The method of claim 49, wherein the pH is about 3.5.

51. A method of preparing a methylnaltrexone formulation, the method comprising the steps of:

preparing a solution comprising methylnaltrexone or a pharmaceutically acceptable salt thereof, an isotonic agent, a calcium salt chelating agent and a stabilizing agent;
adjusting the pH of the solution to between pH 2.0 and pH 6.0; and

sterilizing the resulting solution and distributing to one or more sealed containers.

52. The method of claim 51, wherein the calcium salt chelating agent is selected from the group calcium ethylenediaminetetraacetic acid (EDTA), calcium diethylenetriaminepentaacetic acid (DTPA), calcium hydroxyethylenediaminetriacetic acid (HEDTA), calcium ethylene glycol-bis-(2-aminoethyl)-N,N,N', N'-tetraacetic acid (EGTA), calcium nitrilotriacetic acid (NTA), calcium citrate, and calcium salt derivatives thereof.

53. The method of claim 51, wherein the active compound is methylnaltrexone bromide.

54. The method of claim 51, wherein the isotonic agent is selected from the group consisting of sodium chloride, mannitol, lactose, dextrose, glycerol, and sorbitol.

55. The method of claim 54, wherein the isotonic agent comprises a delivery vehicle selected from the group consisting of 5% Dextrose, Lactated Ringer's Injection and 0.65%NaCl and 0.9% NaCl.

56. The method of claim 51, wherein the aqueous solution comprises water for injection.

57. The method of claim 52, wherein the calcium salt chelating agent is calcium ethylenediaminetriacetic acid (EDTA) or calcium ethylene glycol-bis-(2-aminoethyl)-N,N,N', N'-tetraacetic acid (EGTA), or a calcium salt derivative thereof.

58. The method of claim 51, wherein the stabilizing agent is glycine.

59. The method of claim 58, wherein the glycine is glycine-HCl.

60. The method of claim 51, wherein an effective amount of glycine maintains pH at about 3.0 to about 4.0.

61. The method of claim 60, wherein the pH is about 3.5.

62. A method for reducing the side effects of opioid therapy in a subject receiving opioid treatment or use comprising administering to the subject a regimen formulation according to any one of claims 1, 12, 30, 31, 35, 36, or 37, wherein an effective amount of methylnaltrexone is delivered to the subject.

63. A product comprising a formulation according to any one of claims 1, 12, 30, 31, 35, 36, or 37 in a sealed container.

64. The product of claim 63, wherein the container is selected from a vial, ampoule, a bag, a bottle, a syringe, and a dispenser package.

65. The product of claim 64, wherein the container is a vial, and wherein the vial comprises about 1 mL, about 2 mL, about 5mL, about 10mL, or about 20mL capacity.

66. The product of claim 63, wherein the product comprises a diluent container system.

67. The product of claim 66, wherein the diluent container system is a MINIBAG® Plus diluent container system, or an ADD VANTAGE® diluent container system.

68. The product of claim 64, wherein the product comprises a spikable stopper.

69. The product of claim 64, wherein the product comprises a cartridge for use in connection with a patient controlled analgesia device.

70. The product of claim 63, wherein the product comprises a frozen bag diluent container system.

CLAIMS

1. A pharmaceutical composition consisting of an effective amount of methylnaltrexone, or a pharmaceutically acceptable salt thereof, a calcium salt chelating agent, an isotonic agent, and a glycine stabilizing agent, in an aqueous solution wherein the solution has a pH of between about 2.5 and about pH 6.

2. The composition according to claim 1, wherein the methylnaltrexone is methylnaltrexone bromide.

3. The composition according to claim 2, wherein the methylnaltrexone bromide is provided at a concentration of 20 mg/mL.

4. The composition according to any one of claims 1 to 3, wherein the calcium salt chelating agent is calcium EDTA disodium.

5. The composition according to any one of claims 1 to 4, wherein the isotonic agent is sodium chloride.

6. The composition according to any one of claims 1 to 5, wherein the glycine stabilizing agent is glycine hydrochloride.

7. The composition according to any one of claims 1 to 6, wherein the solution has a pH of about 3.5.

8. A pharmaceutical composition comprising methylnaltrexone bromide, calcium EDTA disodium, sodium chloride, and glycine hydrochloride, in an aqueous solution wherein the solution has a pH of between 2.5 and pH 6.

9. The composition according to any one of claims 2 to 8, wherein the methylnaltrexone bromide is provided at a concentration of 20 mg/ L.

10. The composition according to any one of claims 4 to 9, wherein the calcium EDTA disodium is provided at a concentration of about 0.1 to about 1.0 mg/mL.

11. The composition according to claim 10, wherein the calcium EDTA disodium is provided at a concentration of about 0.4 mg/mL.

12. The composition according to any one of claims 6 to 9, wherein the glycine hydrochloride is provided at a concentration of about 0.05 to about 1.0 mg/mL.

13. The composition according to claim 12, wherein the glycine hydrochloride is provided at a concentration of about 0.3 mg/mL.

14. The composition according to claim 8, wherein the methylnaltrexone bromide is provided at a concentration of about 20 mg/mL, the calcium EDTA disodium is provided at a concentration of about 0.4 mg/mL, the glycine hydrochloride is provided at a concentration of about 0.3 mg/mL, and the solution has a pH of about 2.6 to about 5.0.