CLAIMS

What is claimed is:

1. A method of treating at least one symptom of neurogenic orthostatic hypotension comprising orally administering to a person in need thereof an extended release composition comprising pyridostigmine or a pharmaceutically acceptable salt thereof,

wherein the composition provides extended release of pyridostigmine or a pharmaceutically acceptable salt for at least about 8 hours.

2. The method of claim 1, wherein the at least one symptom is retinal hypoperfusion, muscle hypoperfusion, lung hypoperfusion, cerebral hypoperfusion, myocardial hypoperfusion, nonspecific symptoms, or a combination thereof.

3. The method of claim 2, wherein the retinal hypoperfusion is impaired vision.

4. The method of claim 2, wherein the muscle hypoperfusion is neck pain, shoulder pain, or a combination thereof.

5. The method of claim 2, wherein the lung hypoperfusion is orthostatic dyspnea.

6. The method of claim 2, wherein the cerebral hypoperfusion is dizziness, light headedness, pre-syncope, syncope, difficulty concentrating, headache, cognition, or a combination thereof.

7. The method of claim 2, wherein the myocardial hypoperfusion is angina.

8. The method of claim 2, wherein the nonspecific symptoms are generalized weakness, falls, leg buckling, lethargy, fatigue, nausea, or a combination thereof.

9. A method for treating neurogenic orthostatic hypotension, the method comprising orally administering to a person in need thereof an extended release composition comprising pyridostigmine or a pharmaceutically acceptable salt thereof,

wherein the composition provides extended release of pyridostigmine or a pharmaceutically acceptable salt thereof for at least about 8 hours.

10. A method for treating neurogenic orthostatic hypotension in a person that did not respond to other treatments, the method comprising orally administering to the person an extended release composition comprising pyridostigmine or a pharmaceutically acceptable salt thereof,

wherein the composition provides extended release of pyridostigmine or a pharmaceutically acceptable salt thereof for at least about 8 hours.

11. A method for treating neurogenic orthostatic hypotension in persons that discontinued other treatments because of supine hypertension, the method comprising orally administering to the person an extended release composition comprising pyridostigmine or a pharmaceutically acceptable salt thereof,

wherein the composition provides extended release of pyridostigmine or a pharmaceutically acceptable salt thereof for at least about 8 hours.

12. A method for treating at least one symptom of neurogenic orthostatic hypotension caused by primary autonomic failure beta-hydroxylase deficiency, diabetic autonomic neuropathy, and/or non-diabetic autonomic neuropathy, the method comprising orally administering to a person in need thereof an extended release composition comprising pyridostigmine or a pharmaceutically acceptable salt thereof,

wherein the composition provides extended release of pyridostigmine or a pharmaceutically acceptable salt thereof for at least about 8 hours.

13. The method of claim 12, wherein the primary autonomic failure comprises autonomic failure associated with Parkinson's disease (PD), autonomic failure associated with multiple system atrophy, or pure autonomic failure.

14. The method of claim 12, wherein the at least one symptom comprises orthostatic dizziness, lightheadedness, feeling like you might black out, cognitive slowing, sleepiness, presyncope, and syncope, increased risk of falls, cognitive impairment, or exercise intolerance.

15. A method for treating neurogenic orthostatic hypotension without worsening supine hypertension, the method comprising orally administering to a person in need thereof an

extended release composition comprising pyridostigmine or a pharmaceutically acceptable salt thereof,

wherein the composition provides extended release of pyridostigmine or a pharmaceutically acceptable salt thereof for at least about 8 hours.

16. The method of any one of the previous claims, wherein the composition is suitable for once-a-day administration.

17. The method of any one of the previous claims, wherein the composition is a gastroretentive composition.

18. The method of any one of the previous claims, wherein the composition comprises from about 50 mg to about 300 mg of pyridostigmine or a pharmaceutically acceptable salt thereof.

19. The method of any one of the previous claims, wherein the composition comprises from about 100 mg to about 250 mg of pyridostigmine or a pharmaceutically acceptable salt thereof.

20. The method of any one of the previous claims, wherein the composition comprises about 105 mg or about 205 mg of pyridostigmine or a pharmaceutically acceptable salt thereof.

21. The method of any one of the previous claims, wherein the composition comprises an immediate release portion and an extended release portion.

22. The method of claim 21, wherein the extended release portion comprises a core and a permeable elastic membrane comprising an orifice and surrounding the core.

23. The method of claim 21, wherein the immediate release portion comprises an immediate release drug layer comprising pyridostigmine or a pharmaceutically acceptable salt thereof.

24. The method of claim 22, wherein the core comprises pyridostigmine or a pharmaceutically acceptable salt thereof, an acid, a gas generating agent, a filler, a wicking agent, a swellable water-soluble hydrophilic polymer, or combinations thereof.

25. The method of claim 22, wherein the permeable elastic membrane comprises a plasticizer and a copolymer based on ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride.

26. The method of claim 25, wherein the copolymer is present in an amount of from about 60 wt% to about 95 wt%, based on the total weight of the membrane.

27. The method of any one of the previous claims, wherein the treatment comprises an increase in diastolic blood pressure by at least about 5 mmHg post standing.

28. The method of any one of the previous claims, wherein the treatment comprises an increase in systolic blood pressure by at least about 10 mmHg post standing.

29. A method for treating neurogenic orthostatic hypotension, the method comprising orally administering to a person in need thereof an extended release composition comprising pyridostigmine or a pharmaceutically acceptable salt thereof and midodrine or a pharmaceutically acceptable salt thereof,

wherein the composition provides extended release of pyridostigmine or a pharmaceutically acceptable salt thereof and midodrine or a pharmaceutically acceptable salt thereof for at least about 8 hours.

30. A method for making a gastroretentive dosage form comprising a core and a permeable elastic membrane containing an orifice and surrounding the core, the method comprising:

mixing pyridostigmine or a pharmaceutically acceptable salt thereof with at least one glidant to obtain a drug intermediate blend,

mixing the drug intermediate blend with excipients comprising an acid, a gas generating agent, a wicking agent, a filler, a swellable water soluble polymer, or a combination thereof, into a final blend,

compressing the final blend into a tablet core,

coating the tablet core with a functional coat/permeable elastic membrane comprising at least one copolymer of ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride, and at least one plasticizer, to obtain a membrane coated tablet core, and

drilling an orifice through the membrane/functional coat.

31. A method for making a gastroretentive dosage form comprising an immediate release portion comprising an immediate release drug layer; and an extended release portion comprising a core coated with a permeable elastic membrane comprising an orifice, the method comprising:

mixing pyridostigmine or a pharmaceutically acceptable salt thereof with at least one glidant to obtain a drug intermediate blend,

mixing the drug intermediate blend with excipients comprising an acid(s), a gas generating agent, a wicking agent(s), a filler(s), a swellable water soluble polymer, or a combination thereof, into a final blend,

compressing the final blend into a tablet core,

coating the tablet core with a permeable elastic membrane comprising at least one copolymer of ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride; and at least one plasticizer, to obtain a membrane coated tablet core,

drilling an orifice through the membrane to a obtain membrane coated tablet core comprising an orifice in the membrane, and

coating the membrane coated tablet core comprising an orifice in the membrane with an immediate release drug layer comprising pyridostigmine or a pharmaceutically acceptable salt thereof.

32. An extended release gastroretentive dosage form comprising pyridostigmine or a pharmaceutically acceptable salt thereof, wherein the dosage form is dose proportional at 105 mg, 205mg, 275 mg, and 340 mg strengths, based on PK parameters comprising Cmax.

33. A gastroretentive dosage form comprising an immediate release portion and an extended release portion,

wherein the immediate release portion comprises an immediate release drug layer comprising pyridostigmine or a pharmaceutically acceptable salt thereof,

wherein the extended release portion comprises a core, and a permeable elastic membrane comprising at least one orifice and surrounding the core,

wherein the core comprises a drug intermediate blend; and excipients comprising an acid, a gas-generating agent, a wicking agent, a filler, a swellable water-soluble hydrophilic polymer, or a combination thereof

wherein the drug intermediate blend comprises pyridostigmine or a pharmaceutically acceptable salt thereof and at least one glidant,

wherein the permeable elastic membrane comprises at least one copolymer of ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride; and at least one plasticizer.

34. A gastroretentive dosage form comprising a core, and a permeable elastic membrane comprising at least one orifice and surrounding the core,

wherein the core comprises a drug intermediate blend, and at least one excipient comprising an acid, a gas-generating agent, a wicking agent, a filler, a swellable water-soluble hydrophilic polymer, or a combination thereof,

wherein the drug intermediate blend comprises pyridostigmine or a pharmaceutically acceptable salt thereof and at least one glidant,

wherein the permeable elastic membrane comprises at least one copolymer of ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride; and at least one plasticizer.

35. The dosage form of claim 33 or claim 34, wherein the acid is an organic acid.

36. The dosage form of any one of claims 33-35, wherein the organic acid is selected from the group consisting of succinic acid, citric acid, acetic acid, malic acid, fumaric acid, stearic acid, tartaric acid, boric acid, benzoic acid, and a combination thereof.

37. The dosage form of any one of claims 33-36, wherein the gas generating agent is selected from the group consisting of carbonate and bicarbonate salts of alkali and alkaline earth metals.

38. The dosage form of any one of claims 33-37, wherein the gas generating agent is selected from the group consisting of sodium bicarbonate, sodium carbonate, magnesium carbonate, and calcium carbonate.

39. The dosage form of any one of claims 33-38, wherein the wicking agent is crospovidone.

40. The dosage form of any one of claims 33-39, wherein the filler is selected from the group consisting of lactose monohydrate, anhydrous lactose, directly compressible starches, hydrolyzed starches, pregelatinized starch, microcrystalline cellulose, silicified microcrystalline cellulose, carboxymethylcellulose and other cellulose polymers, sucrose and sucrose-based materials, dextrose, dibasic calcium phosphate anhydrous, dibasic calcium phosphate dihydrate, tricalcium phosphate, calcium sulfate dihydrate, and other alkaline inorganic salts, sugar alcohols such as mannitol, sorbitol, and xylitol, confectioner's sugar, and a combination thereof.

41 The dosage form of any one of claims 33-40, wherein the swellable water-soluble hydrophilic polymer is hydroxypropyl methylcellulose.

42. The dosage form of claim 41, wherein the hydroxypropyl methylcellulose is a mixture low viscosity hydroxypropyl methylcellulose and a high viscosity hydroxypropyl methylcellulose.

43. The dosage form of claim 42, wherein the low viscosity hydroxypropyl methylcellulose has a viscosity of from about 50 mPa·s to about 2,400 mPa·s, and a weight average molecular weight of from about 150,000 Da to about 300,000 Da.

44. The dosage form of claim 42, wherein the high viscosity hydroxypropyl methylcellulose has a viscosity of from about 2,500 mPa·s to about 300,000 mPa·s, and a weight average molecular weight of from about 350,000 Da and about 1,500,000 Da.

45. The dosage form of claim 42, wherein the low viscosity hydroxypropyl methylcellulose and the high viscosity hydroxypropyl methylcellulose are present in equal wt%, based on the total weight of the core.

Claims

1. Use of pyridostigmine or a pharmaceutically acceptable salt thereof in manufacture of medicament for treating at least one symptom of neurogenic orthostatic hypotension, wherein the medicament is to be orally administered in an extended release composition comprising an immediate release component and an extended release component, wherein the immediate release component comprises an immediate release drug layer comprising from about 10 mg to about 100 mg of pyridostigmine or a pharmaceutically acceptable salt thereof,;
wherein the extended release component comprises a core and a permeable elastic membrane comprising an orifice and surrounding the core;
wherein the core comprises from about 50 mg to about 200 mg of pyridostigmine or a pharmaceutically acceptable salt thereof;
wherein the permeable elastic membrane comprises a copolymer based on ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride, and
wherein the copolymer is present in an amount of from about 70 wt% to about 95 wt%, based on total membrane weight.

2. The use of claim 1, wherein the at least one symptom is retinal hypoperfusion, muscle hypoperfusion, myocardial hypoperfusion, nonspecific symptoms, or combinations thereof.

3. The use of claim 2, wherein the retinal hypoperfusion is impaired vision.

4. The use of claim 2, wherein the muscle hypoperfusion is neck pain, shoulder pain, or combinations thereof.

5. The use of claim 2, wherein the lung hypoperfusion is orthostatic dyspnea.

6. The use of claim 2, wherein the cerebral hypoperfusion is dizziness, light headedness, pre-syncope, difficulty concentrating, headache, cognition, or combinations thereof.

7. The use of claim 2, wherein the myocardial hypoperfusion is angina.

8. The use of claim 2, wherein the nonspecific symptoms are generalized weakness, falls, leg buckling, lethargy, fatigue, nausea, or combinations thereof.

9. Use of pyridostigmine or a pharmaceutically acceptable salt thereof in manufacture of medicament for treating neurogenic orthostatic hypotension, wherein the medicament is to be orally administered in an extended release composition comprising an immediate release component and an extended release component, wherein the immediate release component comprises an immediate release drug layer comprising from about 10 mg to about 100 mg of pyridostigmine or a pharmaceutically acceptable salt thereof,;
wherein the extended release component comprises a core and a permeable elastic membrane comprising an orifice and surrounding the core;
wherein the core comprises from about 50 mg to about 200 mg of pyridostigmine or a pharmaceutically acceptable salt thereof;
wherein the permeable elastic membrane comprises a copolymer based on ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride, and
wherein the copolymer is present in an amount of from about 70 wt% to about 95 wt%, based on total membrane weight.

10. Use of pyridostigmine or a pharmaceutically acceptable salt thereof in manufacture of medicament for treating neurogenic orthostatic hypotension in a patient that did not respond to other treatments, wherein the medicament is to be orally administered in an extended release composition comprising an immediate release component and an extended release component, wherein the immediate release component comprises an immediate release drug layer comprising from about 10 mg to about 100 mg of pyridostigmine or a pharmaceutically acceptable salt thereof,;
wherein the extended release component comprises a core and a permeable elastic membrane comprising an orifice and surrounding the core;
wherein the core comprises from about 50 mg to about 200 mg of pyridostigmine or a pharmaceutically acceptable salt thereof;
wherein the permeable elastic membrane comprises a copolymer based on ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride, and

wherein the copolymer is present in an amount of from about 70 wt% to about 95 wt%, based on total membrane weight.

11. Use of pyridostigmine or a pharmaceutically acceptable salt thereof in manufacture of medicament for treating at least one symptom of neurogenic orthostatic hypotension caused by primary autonomic failure beta-hydroxylase deficiency, diabetic autonomic neuropathy, and/or non-diabetic autonomic neuropathy, wherein the medicament is to be orally administered in an extended release composition comprising an immediate release component and an extended release component, wherein the immediate release component comprises an immediate release drug layer comprising from about 10 mg to about 100 mg of pyridostigmine or a pharmaceutically acceptable salt thereof,;
wherein the extended release component comprises a core and a permeable elastic membrane comprising an orifice and surrounding the core;
wherein the core comprises from about 50 mg to about 200 mg of pyridostigmine or a pharmaceutically acceptable salt thereof;
wherein the permeable elastic membrane comprises a copolymer based on ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride, and
wherein the copolymer is present in an amount of from about 70 wt% to about 95 wt%, based on total membrane weight.

12. The use of claim 11, wherein the primary autonomic failure comprises primary autonomic failure associated with Parkinson's disease, autonomic failure associated with multiple system atrophy, or pure autonomic failure.

13. The use of claim 11, wherein the at least one symptom comprises orthostatic dizziness, lightheadedness, feeling of black out, cognitive slowing, sleepiness, presyncope, syncope, increased risk of falls, or exercise intolerance.

14. Use of pyridostigmine or a pharmaceutically acceptable salt thereof in manufacture of medicament for treating neurogenic orthostatic hypotension without worsening supine hypertension, wherein the medicament is to be orally administered in an extended release

composition comprising an immediate release component and an extended release component, wherein the immediate release component comprises an immediate release drug layer comprising from about 10 mg to about 100 mg of pyridostigmine or a pharmaceutically acceptable salt thereof,;
wherein the extended release component comprises a core and a permeable elastic membrane comprising an orifice and surrounding the core;
wherein the core comprises from about 50 mg to about 200 mg of pyridostigmine or a pharmaceutically acceptable salt thereof;
wherein the permeable elastic membrane comprises a copolymer based on ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride, and
wherein the copolymer is present in an amount of from about 70 wt% to about 95 wt%, based on total membrane weight.

15. The use of claim 14, wherein the treatment comprises increasing diastolic blood pressure by at least 5 mm Hg post standing and increasing systolic blood pressure by at least 10 mm Hg post standing.

16. The use of claim 14, wherein the core further comprises an acid; a gas generating agent; a filler; a wicking agent; a swellable, water-soluble, hydrophilic polymer; and or combinations thereof.

17. The use of claim 16, wherein the acid is selected from the group consisting of succinic acid, citric acid, acetic acid, malic acid, fumaric acid, stearic acid, tartaric acid, boric acid, benzoic acid, and combinations thereof.

18. The use of claim 16, wherein the swellable, water-soluble hydrophilic polymer is hydroxypropyl methylcellulose.

19. The use of claim 16, wherein the gas generating agent is selected from the group consisting of sodium bicarbonate, magnesium carbonate, and calcium carbonate, and mixture thereof.

20. The use of claim 16, wherein the wicking agent is crospovidone.