ORIGINAL

ABSTRACT

PHARMACEUTICAL COMPOSITIONS OF COMBINATIONS OF DIPEPTIDYL PEPTIDASE-4 INHIBITORS WITH PIOGLITAZONE

This invention relates to a bilayer pharmaceutical compositions comprising fixed-dose combinations of a dipeptidyl peptidase-4 inhibitor and pioglitazone, methods of preparing such pharmaceutical compositions, and methods of treating Type 2 diabetes with such pharmaceutical compositions.

I/We Claim:

1. A pharmaceutical composition in the form of a bilayer tablet comprising:
(a) a first layer comprising about 20 to 45 % by weight of a dipeptidyl peptidase-4 inhibitor, or a pharmaceutically acceptable salt thereof; and
(b) a second layer comprising about 7 to 24 % by weight of pioglitazone hydrochloride.

2. The pharmaceutical composition of Claim 1 wherein the first layer additionally comprises one or more excipients selected from the group consisting of: (i) a diluent; (ii) a disintegrant; and (iii) a lubricant.

3. The pharmaceutical composition of Claim 2 wherein the first layer additionally comprises a binding agent.

4. The pharmaceutical composition of Claim 1 wherein the first layer additionally comprises excipients selected from the group consisting of: (i) about 40-80 % by weight of a diluent; (ii) about 0.5-6 % by weight of a disintegrant; and (iii) about 0.75-10 % by weight of a lubricant.

5. The pharmaceutical composition of Claim 1 wherein the second layer additionally comprises one or more excipients selected from the group consisting of: (i) a diluent, (ii) a disintegrant; (iii) a binding agent; and (iv) a lubricant.

6. The pharmaceutical composition of Claim 1 wherein the second layer additionally comprises excipients selected from the group consisting of: (i) about 60-80 % by weight of a diluent; (ii) about 2-12 % by weight of a disintegrant; and (iii) about 1-7 % by weight of a binding agent; and (iv) about 0.25-4 % by weight of a lubricant.

7. The pharmaceutical composition of Claim 1 comprising:
(a) a first layer comprising:
   (i) about 20 to 45 % by weight of a dipeptidyl peptidase-4 inhibitor, or a pharmaceutically acceptable salt thereof;
   (ii) about 40-80 % by weight of a diluent;
   (iii) about 0.5-6 % by weight of a disintegrant; and
   (iv) about 0.75-10 % by weight of a lubricant; and
(b) a second layer comprising:
   (i) about 7 to 24 % by weight of pioglitazone hydrochloride;

(ii) about 60-80 % by weight of a diluent;
(iii) about 2-12 % by weight of a disintegrant;
(iv) about 1-7 % by weight of a binding agent, and
(v) about 0.25-4 % by weight of a lubricant.

8. The pharmaceutical composition of Claim 7 wherein the diluent in the first layer is selected from the group consisting of: microcrystalline cellulose, mannitol and anhydrous dibasic calcium phosphate, or a mixture thereof; the disintegrant is selected from the group consisting of: crospovidone and croscarmellose sodium, or a mixture thereof; and the lubricant is selected from the group consisting of: magnesium stearate and sodium stearyl fumarate, or a mixture thereof.

9. The pharmaceutical composition of Claim 7 wherein the diluent in the first layer is a mixture of microcrystalline cellulose and mannitol; the disintegrant is crospovidone; and the lubricant is a mixture of magnesium stearate and sodium stearyl fumarate.

10. The pharmaceutical composition of Claim 7 wherein the diluent in the first layer is a mixture of microcrystalline cellulose and anhydrous dibasic calcium phosphate; the disintegrant is croscarmellose sodium; and the lubricant is a mixture of magnesium stearate and sodium stearyl fumarate.

11. The pharmaceutical composition of Claim 7 wherein the diluent in the second layer is selected from the group consisting of: lactose monohydrate, microcrystalline cellulose and mannitol, or a mixture thereof; the disintegrant is selected from the group consisting of: crospovidone and croscarmellose sodium, or a mixture thereof; the binding agent is hydroxypropyl cellulose; and the lubricant is selected from the group consisting of: magnesium stearate, and sodium stearyl fumarate, or a mixture thereof.

12. The pharmaceutical composition of Claim 7 wherein the diluent in the second layer is lactose monohydrate; the disintegrant is crospovidone; the binding agent is hydroxypropyl cellulose; and the lubricant is magnesium stearate.

13. The pharmaceutical composition of Claim 7 wherein the diluent in the second layer is lactose monohydrate; the disintegrant is crospovidone; the binding agent is hydroxypropyl cellulose; and the lubricant is sodium stearyl fumarate.

14. The pharmaceutical composition of Claim 1 wherein the dipeptidyl peptidase-4 inhibitor is selected from the group consisting of: alogliptin, carmegliptin, denagliptin, dutogliptin, linagliptin, melogliptin, saxagliptin, sitagliptin, and vildagliptin, or a pharmaceutically acceptable salt of each thereof.

15. The pharmaceutical composition of Claim 1 wherein the dipeptidyl peptidase-4 inhibitor is sitagliptin, or the dihydrogenphosphate salt thereof.

16. The pharmaceutical composition of Claim 1 comprising:
(a) a first layer comprising:
(i) about 25 to 35 % by weight of a dipeptidyl peptidase-4 inhibitor, or a pharmaceutically acceptable salt thereof;
(ii) about 50-70 % by weight of a diluent;
(iii) about 1-4 % by weight of a disintegrant; and
(iv) about 1.5-7 % by weight of a lubricant; and
(b) a second layer comprising:
(i) about 12 to 20 % by weight of pioglitazone hydrochloride;
(ii) about 65-75 % by weight of a diluent;
(iii) about 3-11 % by weight of a disintegrant;
(iv) about 2-5 % by weight of a binding agent; and
(v) about 0.5-2.5 % by weight of a lubricant.

17. The pharmaceutical composition of Claim 16 wherein the dipeptidyl peptidase-4 inhibitor in the first layer is sitagliptin, or a pharmaceutically acceptable salt thereof; the diluent is a mixture of microcrystalline cellulose and mannitol, or a mixture of microcrystalline cellulose and anhydrous dibasic calcium phosphate; the disintegrant is croscarmellose sodium or crospovidone; and the lubricant is selected from the group consisting of: magnesium stearate, and sodium stearyl fumarate, or a mixture thereof.

18. The pharmaceutical composition of Claim 16 wherein the diluent in the second layer is lactose monohydrate; the disintegrant is crospovidone; the binding agent is hydroxypropylcellulose; and the lubricant is magnesium stearate.

19. The pharmaceutical composition of Claim 16 wherein the diluent in the second layer is lactose monohydrate; the disintegrant is crospovidone; the binding agent is hydroxypropylcellulose; and the lubricant is sodium stearyl fumarate.

20. The pharmaceutical composition of Claim 16 wherein the dipeptidyl peptidase-4 inhibitor is present in a unit dosage strength of 25, 50, 75, 100, 150, or 200 milligrams, and the pioglitazone is present in a unit dosage strength of 15, 30, or 45 milligrams.

21. The pharmaceutical composition of Claim 16 wherein the dipeptidyl peptidase-4 inhibitor is sitagliptin, or a pharmaceutically acceptable salt thereof.

22. The pharmaceutical composition of Claim 21 wherein the sitagliptin is present in a unit dosage strength of 50 or 100 milligrams, and the pioglitazone is present in a unit dosage strength of 15, 30 or 45 milligrams.

23. The pharmaceutical composition of Claim 1 wherein said composition is in the dosage form of a tablet.

24. A method of treating Type 2 diabetes in a human in need thereof comprising orally administering to said human a pharmaceutical composition of Claim 1.

25. The pharmaceutical composition of Claim 1 further comprising one or more agents selected from the group consisting of flavoring agents, colorants, and sweeteners.

26. The pharmaceutical composition of Claim 1 wherein the bilayer tablet is coated with a film-coating agent.

27. The pharmaceutical composition of Claim 1 wherein said DPP-4 inhibitor is vildagliptin, or a pharmaceutically acceptable salt of each thereof.

28. The pharmaceutical composition of Claim 1 wherein said DPP-4 inhibitor is saxagliptin, or a pharmaceutically acceptable salt of each thereof.

29. The pharmaceutical composition of Claim 1 wherein said DPP-4 inhibitor is alogliptin, or a pharmaceutically acceptable salt of each thereof.

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To,
The Controller of Patents
The Patent Office at **New Delhi**