CLAIMS

1. Use of a biguanide compound in the manufacture of a medicament for lowering blood glucose levels in a patient in need thereof, wherein the biguanide compound is in a delayed-release formulation adapted to minimize the circulating plasma concentration of the biguanide compound and/or reduce the average systemic bioavailability of the biguanide compound in the patient.

2. Use of a biguanide compound in the manufacture of a medicament for treating a disorder of glucose metabolism in a patient in need thereof, wherein the biguanide compound is in a delayed-release formulation adapted to minimize the circulating plasma concentration of the biguanide compound and/or reduce the average systemic bioavailability of the biguanide compound in the patient.

3. The use according to claim 1 or 2, wherein the average systemic bioavailability of the biguanide compound as measured by plasma AUC resulting from administration of the delayed-release formulation is less than the average systemic bioavailability of the biguanide compound as measured by plasma AUC resulting from administration of an immediate release formulation having an equivalent amount of the biguanide compound.

4. The use according to claim 1 or 2, wherein the average systemic bioavailability of the biguanide compound as measured by plasma AUC resulting from administration of the delayed-release formulation is 70%, 60%, 50%, 40%, 30% or 20% less than the average systemic bioavailability of the biguanide compound as measured by plasma AUC resulting from administration of an immediate release formulation having an equivalent amount of the biguanide compound.

5. The use according to claim 1 or 2, wherein the biguanide compound is metformin or a salt thereof.

6. The use according to claim 5, wherein the metformin plasma AUC in the patient resulting from administration of a single dose of the delayed-release formulation is $\leq$ 50% of the metformin plasma AUC resulting from administration of a single dose of GLUMETZA® having an equivalent amount of the metformin or a salt thereof.

7. The use according to claim 6, wherein the amount of the metformin or a salt thereof is 500 mg, and wherein administration of a single dose of the delayed-release formulation provides a metformin plasma AUC in the patient that is $\leq$ 2148.5 ng•hr/mL.

8. The use according to claim 6, wherein the amount of the metformin or a salt thereof is 1000 mg, and wherein administration of a single dose of the delayed-release formulation provides a metformin plasma AUC in the patient that is $\leq$ 4311.5 ng•hr/mL.

9. The use according to claim 6, wherein the amount of the metformin or a salt thereof is 1500 mg, and wherein administration of a single dose of the delayed-release formulation provides a metformin plasma AUC in the patient that is $\leq$ 6066 ng•hr/mL.

10. The use according to claim 6, wherein the amount of the metformin or a salt thereof is 2500 mg, and wherein administration of a single dose of the delayed-release formulation provides a metformin plasma AUC in the patient that is $\leq$ 9296.5 ng•hr/mL.

11. The use according to claim 1 or 2, wherein the amount of the biguanide compound is about 500 mg, and wherein the delayed-release formulation minimizes the circulating plasma concentration of the biguanide compound in the patient below about 1 μg/mL, 0.5 μg/mL, or 0.25 μg/mL.

12. The use according to claim 1 or 2, wherein the amount of the biguanide compound is about 1000 mg, and wherein the delayed-release formulation minimizes the circulating plasma concentration of the biguanide compound in the patient below about 2 μg/mL, 1 μg/mL or 0.5 μg/mL.

13. The use according to claim 1 or 2, wherein the amount of the biguanide compound is about 1500 mg, and wherein the delayed-release formulation minimizes the circulating plasma concentration of the biguanide compound in the patient below about 3 μg/mL, 2 μg/mL or 1 μg/mL.

14. The use according to claim 1 or 2, wherein the delayed-release formulation minimizes the plasma C_{max} level of the biguanide compound.

15. The use according to claim 14, wherein the amount of the biguanide compound is about 1000 mg, and wherein the biguanide compound plasma C_{max} in the patient resulting from administration of the delayed-release formulation is less than about 1000 ng/mL.

16. The use according to claim 1 or 2, wherein the daily dose of the biguanide compound is between about 50 mg and about 1000 mg.

17. The use according to claim 1 or 2, wherein the daily dose of the biguanide compound is between about 100 mg and about 500 mg.

18. The use according to claim 1 or 2, wherein the daily dose of the biguanide compound is about 500 mg.

19. The use according to claim 1 or 2, wherein the daily dose of the biguanide compound is about 600 mg.

20. The use according to claim 1 or 2, wherein the daily dose of the biguanide compound is about 1000 mg.

21. The use according to claim 1 or 2, wherein the biguanide compound is enterically-coated.

22. The use according to claim 1 or 2, wherein the biguanide compound is metformin hydrochloride.

23. The use according to claim 1 or 2, wherein the delayed-release formulation further comprises an antidiabetic agent selected from: thiazolidinediones, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, DPP-IV inhibitors, incretin mimetics, and SGLT inhibitors.

24. The use according to claim 23, wherein the antidiabetic agent is an SGLT inhibitor.

25. The use according to claim 1 or 2, wherein the delayed-release formulation further comprises an antiobesity agent.

26. The use according to claim 25, wherein the antiobesity agent is lorcaserin.

27. The use according to claim 25, wherein the antiobesity agent is phentermine.

28. The use according to claim 25, wherein the antiobesity agent is a combination of lorcaserin and phentermine.

29. The use according to claim 25, wherein the antiobesity agent is a combination of topiramate and phentermine.

30. The use according to claim 25, wherein the antiobesity agent is a combination of bupropion and naltrexone.

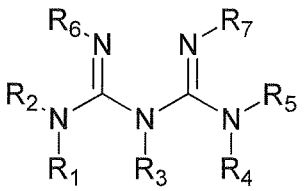
31. The use according to claim 1 or 2, wherein the patient has diabetes.

Claims

1. Use of a biguanide compound in the manufacture of a medicament for lowering blood glucose levels in a patient in need thereof, wherein the biguanide compound is in a delayed-release formulation having an onset of release in the duodenum, jejunum, ileum, caecum, colon and/or rectum of the patient, adapted to minimize the circulating plasma concentration of the biguanide compound and/or reduce the average systemic bioavailability of the biguanide compound in the patient.

2. Use of a biguanide compound in the manufacture of a medicament for treating a disorder of glucose metabolism in a patient in need thereof, wherein the biguanide compound is in a delayed-release formulation having an onset of release in the duodenum, jejunum, ileum, caecum, colon and/or rectum of the patient, adapted to minimize the circulating plasma concentration of the biguanide compound and/or reduce the average systemic bioavailability of the biguanide compound in the patient.

3. The use according to claim 1 or 2, wherein the biguanide compound is selected from compounds of Formula I:



I

wherein:

R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are independently selected from:

H, OH,

O-Rx, wherein Rx is alkyl, cycloalkyl, alkylcycloalkyl, acyl, ester, thioester;

optionally substituted alkyl (e.g., a C_1 to C_{12} straight chain or branched chain alkyl optionally substituted with oxygen, silicon, sulphur or optionally substituted with OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl); cycloalkyl (e.g., C_3 to C_7 cycloalkyl); alkylcycloalkyl (e.g., C_4 to C_{12} alkylcycloalkyl); heterocycloalkyl (e.g., where the heterocycle comprises one or two hetero atoms selected from O, S, or N, including a C_2 to C_6 heterocycloalkyl); alkylheterocycloalkyl (e.g., where the heterocycle comprises one or two hetero atoms selected from O, S, or N, including a C_3 to C_{11} alkylheterocycloalkyl, and including wherein when N is present in the heterocyclic ring, the nitrogen atom may be in the form of an amide, carbamate or urea); optionally substituted alkenyl (e.g., C_1 to C_{12} straight chain or branched chain

alkenyl optionally substituted with oxygen, silicon, sulphur or optionally substituted with OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl); optionally substituted alkynyl (e.g., C_1 to C_{12} straight chain or branched chain alkynyl optionally substituted with oxygen, silicon, sulphur or optionally substituted with OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl);

optionally substituted aryl (e.g., phenyl, substituted phenyl, naphthyl, substituted naphthyl); optionally substituted alkylaryl (e.g., alkylphenyl, alkyl substituted phenyl, alkylnaphthyl, alkyl substituted naphthyl); optionally substituted heteroaryl (e.g., pyridyl, furanyl, thiophenyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, diazolyl, pyrazolyl, triazolyl all of which are optionally substituted); optionally substituted alkylheteroaryl; and

or R_6 and R_7 may join to form a bond, together forming a ring including the nitrogen atoms to which they are attached;

or R_1 and R_2 may together form a 3 to 8 membered heterocyclic ring, including the nitrogen atoms to which they are attached;

or R_4 and R_5 may together form a ring selected from the group aziridine, pyrrolyl, imidazolyl, pyrazolyl, indolyl, indolinyl, pyrrolidinyl, piperazinyl and piperidyl, including the nitrogen atoms to which they are attached.

4. The use according to any one of claims 1 to 3, wherein the average systemic bioavailability of the biguanide compound as measured by plasma AUC resulting from administration of the delayed-release formulation is less than the average systemic bioavailability of the biguanide compound as measured by plasma AUC resulting from administration of an immediate release formulation having an equivalent amount of the biguanide compound.

5. The use according to any one of claims 1 to 3, wherein the average systemic bioavailability of the biguanide compound as measured by plasma AUC resulting from administration of the delayed-release formulation is 70%, 60%, 50%, 40%, 30% or 20% less than the average systemic bioavailability of the biguanide compound as measured by plasma AUC resulting from administration of an immediate release formulation having an equivalent amount of the biguanide compound.

6. The use according to any one of claims 1 to 3, wherein the biguanide compound is metformin or a salt thereof.

7. The use according to claim 6, wherein the metformin plasma AUC in the patient resulting from administration of a single dose of the delayed-release formulation is $\leq$ 50% of the metformin plasma AUC resulting from administration of a single dose of GLUMETZA® having an equivalent amount of the metformin or a salt thereof.

8. The use according to claim 7, wherein the amount of the metformin or a salt thereof is 500 mg, and wherein administration of a single dose of the delayed-release formulation provides a metformin plasma AUC in the patient that is $\leq$ 2148.5 ng•hr/mL.

9. The use according to claim 7, wherein the amount of the metformin or a salt thereof is 1000 mg, and wherein administration of a single dose of the delayed-release formulation provides a metformin plasma AUC in the patient that is $\leq$ 4311.5 ng•hr/mL.

10. The use according to claim 7, wherein the amount of the metformin or a salt thereof is 1500 mg, and wherein administration of a single dose of the delayed-release formulation provides a metformin plasma AUC in the patient that is $\leq$ 6066 ng•hr/mL.

11. The use according to claim 7, wherein the amount of the metformin or a salt thereof is 2500 mg, and wherein administration of a single dose of the delayed-release formulation provides a metformin plasma AUC in the patient that is $\leq$ 9296.5 ng•hr/mL.

12. The use according to any one of claims 1 to 3, wherein the amount of the biguanide compound is about 500 mg, and wherein the delayed-release formulation minimizes the circulating plasma concentration of the biguanide compound in the patient below about 1 μg/mL, 0.5 μg/mL, or 0.25 μg/mL.

13. The use according to any one of claims 1 to 3, wherein the amount of the biguanide compound is about 1000 mg, and wherein the delayed-release formulation minimizes the circulating plasma concentration of the biguanide compound in the patient below about 2 μg/mL, 1 μg/mL or 0.5 μg/mL.

14. The use according to any one of claims 1 to 3, wherein the amount of the biguanide compound is about 1500 mg, and wherein the delayed-release formulation minimizes the circulating plasma concentration of the biguanide compound in the patient below about 3 μg/mL, 2 μg/mL or 1 μg/mL.

15. The use according to any one of claims 1 to 3, wherein the delayed-release formulation minimizes the plasma C_{max} level of the biguanide compound.

16. The use according to claim 15, wherein the amount of the biguanide compound is about 1000 mg, and wherein the biguanide compound plasma C_{max} in the patient resulting from administration of the delayed-release formulation is less than about 1000 ng/mL.

17. The use according to any one of claims 1 to 3, wherein the daily dose of the biguanide compound is between about 10 mg to about 1500 mg.

18. The use according to any one of claims 1 to 3, wherein the daily dose of the biguanide compound is between about 50 mg and about 1000 mg.

19. The use according to any one of claims 1 to 3, wherein the daily dose of the biguanide compound is between about 100 mg and about 500 mg.

20. The use according to any one of claims 1 to 3, wherein the daily dose of the biguanide compound is about 500 mg.

21. The use according to any one of claims 1 to 3, wherein the daily dose of the biguanide compound is about 600 mg.

22. The use according to any one of claims 1 to 3, wherein the daily dose of the biguanide compound is about 1000 mg.

23. The use according to any one of claims 1 to 3, wherein the daily dose of the biguanide compound is about 1500 mg.

24. The use according to any one of claims 1 to 3, wherein the biguanide compound is enterically-coated.

25. The use according to any one of claims 1 to 3, wherein the delayed-release formulation has an onset of release at pH 5.5.

26. The use according to any one of claims 1 to 3, wherein the delayed-release formulation has an onset of release at pH 6.0.

27. The use according to any one of claims 1 to 3, wherein the delayed-release formulation has an onset of release at pH 6.5.

28. The use according to any one of claims 1 to 3, wherein the delayed-release formulation has an onset of release at pH 7.0.

29. The use according to any one of claims 1 to 3, wherein the biguanide compound is metformin hydrochloride.

30. The use according to any one of claims 1 to 3, wherein the delayed-release formulation further comprises an antidiabetic agent selected from: thiazolidinediones, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, DPP-IV inhibitors, incretin mimetics, and SGLT inhibitors.

31. The use according to claim 30, wherein the antidiabetic agent is an SGLT inhibitor.

32. The use according to any one of claims 1 to 3, wherein the delayed-release formulation further comprises an antiobesity agent.

33. The use according to claim 32, wherein the antiobesity agent is lorcaserin.

34. The use according to claim 32, wherein the antiobesity agent is phentermine.

35. The use according to claim 32, wherein the antiobesity agent is a combination of lorcaserin and phentermine.

36. The use according to claim 32, wherein the antiobesity agent is a combination of topiramate and phentermine.

37. The use according to claim 32, wherein the antiobesity agent is a combination of bupropion and naltrexone.

38. The use according to any one of claims 1 to 3, wherein the patient has diabetes.