relative bioavailability in said delayed-release formulation in comparison with an immediate-release formulation having the same amount of said biguanide compound

In another aspect, there is provided the use of a biguanide compound for the manufacture of a medicament for treating a diabetic patient having congestive heart failure, a hypoxic state and/or advanced liver disease, wherein said medicament is in a delayed-release formulation, and said biguanide compound has a reduced relative bioavailability in said delayed-release formulation in comparison with an immediate-release formulation having the same amount of said biguanide compound.

In another aspect, there is provided the use of a biguanide compound for the manufacture of a medicament for treating metabolic disorders in a patient in need thereof, wherein said patient has hyperglycemia and a contraindication for said biguanide compound, wherein said medicament comprises a delayed-release formulation adapted to release said biguanide compound in the distal small intestine and provide a reduced relative bioavailability as measured by plasma area under the curve (AUC) in said delayed-release formulation in comparison with an immediate-release formulation having the same amount of said biguanide compound.

In another aspect, there is provided the use of a biguanide compound for the manufacture of a medicament for treating a patient having diabetes and moderate or severe renal impairment, wherein said medicament comprises a delayed-release formulation adapted to release said biguanide compound in the distal small intestine and provide a reduced relative bioavailability as measured by plasma area under the curve (AUC) in said delayed-release formulation in comparison with an immediate-release formulation having the same amount of said biguanide compound.

In another aspect, there is provided the use of a biguanide compound for the manufacture of a medicament for treating a diabetic patient having congestive heart failure, a hypoxic state and/or advanced liver disease, wherein said medicament comprises a delayed-release formulation adapted to release said biguanide compound in the distal small intestine and provide a reduced relative bioavailability as measured by plasma area under the curve (AUC) in said delayed-release formulation in comparison with an immediate-release formulation having the same amount of said biguanide compound.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] FIG. 1 shows the design of the study described in Example 1.

[0031] FIG. 2 shows the events during the treatment period of the study described in Example 1.

[0032] FIG. 3 shows the plasma concentration of metformin immediate-release (Metformin IR) (●) and metformin delayed-release (Metformin DR) (■) (x-axis; ng/mL) as a function of time (y-axis; min) after ingestion at t = -240 and after a meal at t = 0 min.

CLAIMS

1. Use of a biguanide compound for the manufacture of a medicament for improving the gastrointestinal tolerability of, and/or reducing gastrointestinal complications resulting from, biguanide administration, in a patient having hyperglycemia, wherein said medicament is in a delayed-release formulation, and said biguanide compound has a reduced relative bioavailability in said delayed-release formulation in comparison with an immediate-release formulation having the same amount of said biguanide compound.

2. Use of a biguanide compound for the manufacture of a medicament for treating metabolic disorders in a patient having hyperglycemia and a contraindication for said biguanide compound, wherein said medicament comprises a delayed-release formulation, and said biguanide compound has a reduced relative bioavailability in said delayed-release formulation in comparison with an immediate-release formulation having the same amount of said biguanide compound.

3. The use according to claim 2, wherein said patient has a contraindication selected from the group consisting of a hypoxic condition, impaired lactate clearance, and impaired clearance of said biguanide compound.

4. The use according to claim 3, wherein said patient has a hypoxic condition.

5. The use according to claim 3, wherein said patient has impaired lactate clearance.

6. The use according to claim 3, wherein said patient has impaired clearance of said biguanide compound.

7. The use according to claim 3, wherein said patient has moderate renal impairment, severe renal impairment, or endstage renal disease which results in impaired clearance of said biguanide compound.

8. The use according to claim 3, wherein said patient has chronic kidney disease.

9. The use according to any one of claims 1 to 8, wherein said hyperglycemia is chronic.

10. The use according to claim 9, wherein said hyperglycemia is caused by type II diabetes.

11. Use of a biguanide compound for the manufacture of a medicament for treating a renally impaired patient having diabetes, wherein said medicament is in a delayed-release formulation, and said biguanide compound has a reduced relative bioavailability in said delayed-release formulation in comparison with an immediate-release formulation having the same amount of said biguanide compound.

12. Use of a biguanide compound for the manufacture of a medicament for treating a diabetic patient having congestive heart failure, a hypoxic state and/or advanced liver disease, wherein said medicament is in a delayed-release formulation, and said biguanide compound has a reduced relative bioavailability in said delayed-release formulation in comparison with an immediate-release formulation having the same amount of said biguanide compound.

13. The use according to any one of claims 1 to 12, wherein said medicament produces a mean plasma AUC_{0-36} of said biguanide compound of less than about 15,000, 14,000 or 12,000 ng*h/mL when said medicament is administered to said patient at 1000 mg or less once daily.

14. The use according to any one of claims 1 to 12, wherein said medicament produces a mean plasma C_{max} of said biguanide compound of less than about 1000, 900 or 800 ng/mL when said medicament is administered to said patient at 1000 mg or less once daily.

15. The use according to any one of claims 1 to 12, wherein said biguanide compound has a reduced relative bioavailability of about 40, 50 or 60% in said medicament in comparison with an immediate-release formulation having the same amount of said biguanide compound.

16. The use according to any one of claims 1 to 12, wherein said medicament produces a mean plasma AUC_{0-36} of said biguanide compound of less than about 14,000, 13,000 or 12,000 ng*h/mL when said medicament is administered to said patient at 500 mg twice daily.

17. The use according to any one of claims 1 to 12, wherein said medicament produces a mean plasma C_{max} of said biguanide compound of less than about 800, 700 or 600 ng/mL when said medicament is administered to said patient at 500 mg twice daily.

18. The use according to any one of claims 1 to 17, wherein said biguanide compound is targeted for delivery to the small intestine, and said medicament comprises an oral dosage form enterically coated to release said biguanide compound at a pH at or above 5.0 or 5.5.

19. The use according to claim 18, wherein said biguanide compound is targeted for delivery to the distal small intestine, and said medicament comprises an oral dosage form enterically coated to release said biguanide compound at a pH at or above 6.0 or 6.5.

20. The use according to claim 18 or 19, wherein said medicament is for use in combination with a modified release formulation of said biguanide compound.

21. The use according to claim 18 or 19, wherein said oral dosage form comprises less than 500 mg of said biguanide compound.

22. The use according to any one of claims 1 to 21, wherein said biguanide compound is selected from the group consisting of metformin, phenformin, buformin and imeglimin.

23. The use according to any one of claims 1 to 21, wherein said biguanide compound is metformin hydrochloride.

24. The use according to any one of claims 1 to 23, wherein said medicament is for use in combination with a DPP-IV inhibitor.

25. The use according to any one of claims 1 to 23, wherein said medicament is for use in combination with an anti-obesity or anti-diabetes agent.

CLAIMS

1. Use of a biguanide compound for the manufacture of a medicament for treating metabolic disorders in a patient in need thereof, wherein said patient has hyperglycemia and a contraindication for said biguanide compound, wherein said medicament comprises a delayed-release formulation adapted to release said biguanide compound in the distal small intestine and provide a reduced relative bioavailability as measured by plasma area under the curve (AUC) in said delayed-release formulation in comparison with an immediate-release formulation having the same amount of said biguanide compound.

2. The use according to claim 1, wherein said patient has a contraindication selected from the group consisting of a hypoxic condition, impaired lactate clearance, and impaired clearance of said biguanide compound.

3. The use according to claim 2, wherein said patient has a hypoxic condition.

4. The use according to claim 2, wherein said patient has impaired lactate clearance.

5. The use according to claim 2, wherein said patient has impaired clearance of said biguanide compound.

6. The use according to claim 2, wherein said patient has moderate renal impairment, severe renal impairment, or endstage renal disease which results in impaired clearance of said biguanide compound.

7. The use according to claim 2, wherein said patient has chronic kidney disease.

8. The use according to any one of claims 1 to 7, wherein said hyperglycemia is chronic.

9. The use according to claim 8, wherein said hyperglycemia is caused by type II diabetes.

10. Use of a biguanide compound for the manufacture of a medicament for treating a patient having diabetes and moderate or severe renal impairment, wherein said medicament comprises a delayed-release formulation adapted to release said biguanide compound in the distal small intestine and provide a reduced relative bioavailability as measured by plasma area under the curve (AUC) in said delayed-release formulation in comparison with an immediate-release formulation having the same amount of said biguanide compound.

11. Use of a biguanide compound for the manufacture of a medicament for treating a diabetic patient having congestive heart failure, a hypoxic state and/or advanced liver disease, wherein said medicament comprises a delayed-release formulation adapted to release said biguanide compound in the distal small intestine and provide a reduced relative bioavailability as measured by plasma area under the curve (AUC) in said delayed-release formulation in comparison with an immediate-release formulation having the same amount of said biguanide compound.

12. The use according to any one of claims 1 to 11, wherein said medicament produces a mean plasma AUC_{0-36} of said biguanide compound of less than about 15,000, 14,000, 13,000, or 12,000 ng*h/mL when said medicament is administered to said patient at 1000 mg or less once daily.

13. The use according to any one of claims 1 to 11, wherein said medicament produces a mean plasma C_{max} of said biguanide compound of less than about 1100, 1000, or 900 ng/mL when said medicament is administered to said patient at 1000 mg or less once daily.

14. The use according to any one of claims 1 to 11 wherein said biguanide compound has a reduced relative bioavailability of about 40, 50 or 60% in said delayed-release formulation in comparison with an immediate-release formulation having the same amount of said biguanide compound.

15. The use according to any one of claims 1 to 11, wherein said medicament produces a mean plasma AUC_{0-36} of said biguanide compound of less than about 14,000, 13,000 or 12,000 ng*h/mL when said medicament is administered to said patient at 500 mg twice daily.

16. The use according to any one of claims 1 to 11, wherein said medicament produces a mean plasma C_{max} of said biguanide compound of less than about 800, 700 or 600 ng/mL when said medicament is administered to said patient at 500 mg twice daily.

17. The use according to any one of claims 1 to 16, wherein said biguanide compound is targeted for delivery to the small intestine, and said medicament comprises an oral dosage form enterically coated to release said biguanide compound at a pH of about 6.5.

18. The use according to claim 17, wherein said biguanide compound is targeted for delivery to the distal small intestine, and said medicament comprises an oral dosage form enterically coated to release said biguanide compound at a pH of about 7.0.

19. The use according to claim 17 or 18, wherein said medicament is for use in combination with a modified release formulation of said biguanide compound.

20. The use according to claim 17 or 18, wherein said oral dosage form comprises less than 500 mg of said biguanide compound.

21. The use according to any one of claims 1 to 20, wherein said biguanide compound is selected from the group consisting of metformin, phenformin, buformin and imeglimin.

22. The use according to any one of claims 1 to 20, wherein said biguanide compound is metformin hydrochloride.

23. The use according to any one of claims 1 to 20, wherein said biguanide compound is metformin or a salt thereof.

24. The use according to any one of claims 1-23, wherein the administration of said delayed-release formulation produces a mean plasma AUC0-36 less than about 14,000, 13,000 or 12,000 ng*h/mL when said formulation is administered at 500 mg twice daily.

25. The use according to any one of claims 1-23, wherein the mean plasma C_{max} of said biguanide is less than about 1100 ng/ml when administered at 1000 mg total daily dose (TDD), 500 mg bis in die ("BID") or lower effective doses.

26. The use according to any one of the previous claims, wherein the circulating plasma concentration of said biguanide compound in said patient resulting from administration of said delayed-release formulation is below about 1.0 μg/mL.

27. The use according to any one of the previous claims, wherein the circulating plasma concentration of said biguanide compound in said patient resulting from administration of said delayed-release formulation is below about 0.50 μg/mL.

28. The use according to any one of the previous claims, wherein the circulating plasma concentration of said biguanide compound in said patient resulting from administration of said delayed-release formulation is below about 0.25 μg/mL.

29. The use according to any one of the previous claims, wherein said medicament further comprises a second antidiabetic agent selected from: thiazolidinediones, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, a DPP-IV inhibitor, incretin mimetics, and SGLT inhibitors.

30. The use according to claim 29, wherein said medicament further comprises a DPP-IV inhibitor.

31. The use according to claim 29, wherein said DPP-IV inhibitor is selected from the group consisting of sitagliptin, saxagliptin, berberine, vildagliptin, linagliptin, and alogliptin.

32. The use according to claim 29, wherein said medicament further comprises an SGLT inhibitor.

33. The use according to any one of the previous claims, wherein said medicament further comprises an anti-obesity agent or anti-diabetes agent.

34. The use according to claim 33, wherein said antiobesity agent is lorcaserin.

35. The use according to claim 33, wherein said antiobesity agent is phentermine.

36. The use according to claim 33, wherein said antiobesity agent is a combination of lorcaserin and phentermine.

37. The use according to claim 33, wherein said antiobesity agent is a combination of topiramate and phentermine.

38. The use according to claim 33, wherein said antiobesity agent is a combination of bupropion and naltrexone.