In another aspect, there is provided the use of a biguanide compound in the manufacture of a medicament for treating a renally impaired patient having diabetes, wherein the biguanide compound is in a delayed-release formulation.

In another aspect, there is provided the use of a biguanide compound in the manufacture of a medicament for treating a diabetic patient having congestive heart failure, a hypoxic state and/or advanced liver disease, wherein the biguanide compound is in a delayed-release formulation.

In another aspect, there is provided the use of a biguanide compound in the manufacture of a medicament for reducing the onset of diabetes in a patient with pre-diabetes, wherein the biguanide compound is in a delayed-release formulation.

In another aspect, there is provided the use of a biguanide compound in the manufacture of a medicament for inducing weight loss in a patient, wherein the biguanide compound is in a delayed-release formulation.

In another aspect, there is provided the 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.

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 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.

In another aspect, there is provided the 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

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.

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.

1. Use of a biguanide compound in the manufacture of a medicament for improving the gastrointestinal tolerability of, and/or reducing gastrointestinal complications resulting from, biguanide administration, in a patient, wherein the biguanide compound is in a delayed-release formulation.

2. Use of a biguanide compound in the manufacture of a medicament for treating metabolic disorders in a patient having a contraindication for the biguanide compound, wherein the biguanide compound is in a delayed-release formulation.

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

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

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

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

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

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

9. The use according to claim 1, wherein the patient has hyperglycemia.

10. The use according to claim 9, wherein the hyperglycemia is chronic.

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

12. Use of a biguanide compound in the manufacture of a medicament for treating a renally impaired patient having diabetes, wherein the biguanide compound is in a delayed-release formulation.

13. Use of a biguanide compound in the manufacture of a medicament for treating a diabetic patient having congestive heart failure, a hypoxic state and/or advanced liver disease, wherein the biguanide compound is in a delayed-release formulation.

14. Use of a biguanide compound in the manufacture of a medicament for reducing the onset of diabetes in a patient with pre-diabetes, wherein the biguanide compound is in a delayed-release formulation.

15. Use of a biguanide compound in the manufacture of a medicament for inducing weight loss in a patient, wherein the biguanide compound is in a delayed-release formulation.

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

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

18. The use according to any one of claims 1 to 15, which produces a mean plasma C_{max} of the biguanide compound of less than about 800, 700 or 600 ng/mL when the delayed-release formulation is administered to the patient at 500 mg twice daily.

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

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

21. The use according to claim 19 or 20, for use in combination with a modified release formulation of the biguanide compound.

22. The use according to claim 19 or 20, wherein the oral dosage form comprises less than 500 mg of the biguanide compound.

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

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

25. The use according to any one of claims 1 to 24, for use in combination with a DPP-IV inhibitor.

26. The use according to any one of claims 1 to 24, for use in combination with an anti-obesity or anti-diabetes agent.