SUMMARY OF THE INVENTION

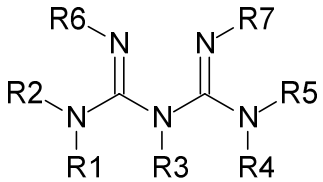
[0006a] In one aspect, provided herein is use of metformin or a salt thereof in the manufacture of a medicament for lowering blood glucose levels in a patient in need thereof, wherein the medicament is a delayed-release formulation, so as to have an onset of release in the intestines (that is, duodenum, jejunum, ileum, caecum, colon and/or rectum), adapted to provide from 20% to 70% less relative bioavailability of metformin as measured by plasma area under curve (AUC) compared to an immediate release composition having the same amount of said metformin or salt thereof.

[0006b] In another aspect, provided herein is use of metformin or a salt thereof in the manufacture of a medicament for treating diabetes in a patient in need thereof, wherein the medicament is a delayed-release formulation, so as to have an onset of release in the intestines (that is, duodenum, jejunum, ileum, caecum, colon and/or rectum), adapted to provide from 20% to 70% less relative bioavailability of metformin as measured by plasma area under curve (AUC) compared to an immediate release composition having the same amount of said metformin or salt thereof.

[0007] Provided herein are compositions having at least one biguanide or related heterocyclic compound, including metformin, and methods of treatment using the compositions.

[0008] In some embodiments, the compositions herein are adapated to minimize the systemic bioavailability of the compound, e.g., reduce average systemic bioavailability of the biguanide compared to a composition having an equivalent amount of the compound formulated for immediate release. In some embodiments, the compositions described herein can be adapted for release to the upper or small intestine, to the lower or large intestine, or both. Administration of the compositions into the intestine is via any known method including oral. In some embodiments, the compositions described herein comprise a biguanide or related heterocyclic compound adapted to release a therapeutically effective amount of the biguanide or related heterocyclic compound beyond the stomach.

[0009] In certain embodiments, the biguanide or related heterocyclic compound is selected from a compound of structural Formula I,



(I)

wherein:

R1, R2, R3, R4, R5, R6, and R7 are independently selected from:

H, OH,

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

optionally substituted alkyl; cycloalkyl; alkylcycloalkyl; heterocycloalkyl; alkylheterocycloalkyl; optionally substituted alkenyl; optionally substituted alkynyl;

optionally substituted aryl; optionally substituted alkylary; optionally substituted heteroaryl; optionally substituted alkylheteroaryl; and

or R6 and R7 may join to form a bond, together forming a ring including the nitrogen atoms to which they are attached;

CLAIMS

WHAT IS CLAIMED IS:

1. Use of metformin or a salt thereof in the manufacture of a medicament for lowering blood glucose levels in a patient in need thereof, wherein the medicament is a delayed-release formulation, so as to have an onset of release in the intestines (that is, duodenum, jejunum, ileum, caecum, colon and/or rectum), adapted to provide from 20% to 70% less relative bioavailability of metformin as measured by plasma area under curve (AUC) compared to an immediate release composition having the same amount of said metformin or salt thereof.

2. Use of metformin or a salt thereof in the manufacture of a medicament for treating diabetes in a patient in need thereof, wherein the medicament is a delayed-release formulation, so as to have an onset of release in the intestines (that is, duodenum, jejunum, ileum, caecum, colon and/or rectum), adapted to provide from 20% to 70% less relative bioavailability of metformin as measured by plasma area under curve (AUC) compared to an immediate release composition having the same amount of said metformin or salt thereof.

3. The use according to claim 1 or 2, wherein said delayed-release formulation is adapted to have an onset of release of said metformin or salt thereof distal of the duodenum.

4. The use according to claim 3, wherein said delayed-release formulation is adapted to have an onset of release of said metformin or salt thereof distal of the jejunum.

5. The use according to claim 4, wherein said delayed-release formulation is adapted to have an onset of release of said metformin or salt thereof distal of the ileum.

6. The use according to any one of claims 1 - 5, wherein said delayed-release formulation comprises an enteric coating.

7. The use according to any one of claims 1 - 6, wherein said delayed-release formulation has an onset of release of said metformin or salt thereof from about pH 6.0 to about pH 8.0.

8. The use according to claim 7, wherein said delayed-release formulation has an onset of release of said metformin or salt thereof from about pH 6.0 to about pH 7.0.

9. The use according to claim 8, wherein said delayed-release formulation has an onset of release of said metformin or salt thereof at a pH of about 6.0.

10. The use according to claim 8, wherein said delayed-release formulation has an onset of release of said metformin or salt thereof at a pH of about 6.5.

11. The use according to claim 8, wherein said delayed-release formulation has an onset of release of said metformin or salt thereof at a pH of about 7.0.

12. The use according to any one of claims 1 - 11, wherein said delayed-release formulation is adapted to provide a circulating plasma concentration of metformin below 1.0 µg/mL.

13. The use according to claim 12, wherein said delayed-release formulation is adapted to provide a circulating plasma concentration of metformin below 0.5 µg/mL.

14. The use according to claim 13, wherein said delayed-release formulation is adapted to provide a circulating plasma concentration of metformin below 0.25 µg/mL.

15. The use according to any one of claims 1 - 14, wherein said medicament is to be administered at a daily dose of said metformin or salt thereof between about 200 mg and about 2000 mg.

16. The use according to claim 15, wherein the daily dose of said metformin or salt thereof is between about 500 mg and about 2000 mg.

17. The use according to claim 16, wherein the daily dose of said metformin or salt thereof is between about 1500 mg and about 2000 mg.

18. The use according to any one of claims 1 - 17, wherein said delayed-release formulation is adapted to provide from 30% to 70% less relative bioavailability of metformin compared to an immediate release composition having the same amount of said metformin or salt thereof.

19. The use according to claim 18, wherein said delayed-release formulation is adapted to provide from 40% to 70% less relative bioavailability of metformin compared to an immediate release composition having the same amount of said metformin or salt thereof.

20. The use according to claim 19, wherein said delayed-release formulation is adapted to provide from 50% to 70% less relative bioavailability of metformin compared to an immediate release composition having the same amount of said metformin or salt thereof.

21. The use according to any one of claims 1 - 20, wherein said metformin or salt thereof is metformin hydrochloride.