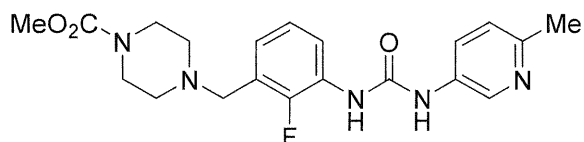


[0005] U.S. Patent No. 7,507,735, herein incorporated by reference, discloses a genus of compounds, including omecamtiv mecarbil (AMG 423, CK-1827452), having the structure:



[0006] Omecamtiv mecarbil is a first in class direct activator of cardiac myosin, the motor protein that causes cardiac contraction. It is being evaluated as a potential treatment of heart failure in both intravenous and oral formulations with the goal of establishing a new continuum of care for patients in both the in-hospital and outpatient settings.

[0007] Clinical trials providing an I.V. delivery of omecamtiv mecarbil have shown that plasma levels of the drug can be delivered safely and effectively. However, standard release formulations and some extended release formulations gave peak to trough ratios that may be too great to provide a safe and effective amount of omecamtiv mecarbil to patients who need the drug in a chronic or preventative setting (See, Figure 4). Accordingly, an effective sustained release formulation would be desirable for increased patient safety and effectiveness.

SUMMARY

[0008] Provided is a pharmaceutical formulation comprising:

- a pharmaceutically acceptable salt of omecamtiv mecarbil, or a pharmaceutically acceptable hydrate thereof;

- a control release agent;

- a pH modifying agent selected from the group consisting of maleic acid, fumaric acid, tartaric acid, glutamic acid, and any combination thereof; a filler; and

- a lubricant.

[0009] Also provided is a process for making a pharmaceutical formulation comprising:

- blending a mixture comprising a pharmaceutically acceptable salt of omecamtiv mecarbil, or a pharmaceutically acceptable hydrate thereof, a control release agent, a pH modifying agent, and a filler;

- lubricating the blended mixture using a lubricant;

- granulating the lubricated blend;

- lubricating the resultant granulation using the lubricant; and

- compressing the lubricated granulation into desired form.

What is Claimed:

1. A pharmaceutical formulation comprising:
 - a pharmaceutically acceptable salt of omecamtiv mecarbil, or a pharmaceutically acceptable hydrate thereof;
 - a control release agent;
 - a pH modifying agent selected from the group consisting of maleic acid, fumaric acid, tartaric acid, glutamic acid, and any combination thereof;
 - a filler; and
 - a lubricant.
2. The pharmaceutical formulation of claim 1, wherein the pharmaceutically acceptable salt of omecamtiv mecarbil or pharmaceutically acceptable hydrate thereof is omecamtiv mecarbil dihydrochloride hydrate.
3. A pharmaceutical formulation according to Claim 1 or 2, wherein the pH modifying agent is fumaric acid or tartaric acid.
4. A pharmaceutical formulation according to Claim 3, wherein the pH modifying agent is fumaric acid.
5. A pharmaceutical formulation according to any one of Claims 1-4, wherein the filler is selected from starches, lactose, mannitol, cellulose derivatives, calcium phosphate, a sugar, and any combination thereof.
6. A pharmaceutical formulation according to any one of Claims 1-5, wherein the control release agent comprises hypromellose having a viscosity of 100,000 mPa.s at 2% concentration in water at 20°C.
7. A pharmaceutical formulation according to any one of Claims 1-5, wherein the control release agent comprises hypromellose having a viscosity of 100 mPa.s at 2% concentration in water at 20°C.

8. A pharmaceutical formulation according to any one of Claims 1-5, wherein the control release agent is a mixture of hypromellose having a viscosity of 100,000 mPa.s at 2% concentration in water at 20°C and hypromellose having a viscosity of 100 mPa.s at 2% concentration in water at 20°C.
9. A pharmaceutical formulation according to any one of Claims 1-8, wherein the filler is a combination of microcrystalline cellulose and lactose monohydrate.
10. A pharmaceutical formulation according to any one of Claims 1-9, wherein the lubricant is magnesium stearate.
11. A pharmaceutical formulation according to any one of Claims 1-10, wherein the formulation is in the form of a tablet.
12. The pharmaceutical formulation according to any one of Claims 1-11 comprising:
 - 3-30% w/w of a pharmaceutically acceptable salt of omecamtiv mecarbil, or a pharmaceutically acceptable hydrate thereof;
 - 15-35% w/w control release agent;
 - 20-45% w/w pH modifying agent;
 - 25-65% w/w filler; and
 - 0.1-1.0% w/w lubricant.
13. A process for making a pharmaceutical formulation according to Claim 1, comprising:
 - blending a mixture comprising a pharmaceutically acceptable salt of omecamtiv mecarbil, or a pharmaceutically acceptable hydrate thereof, a control release agent, a pH modifying agent, and a filler;
 - lubricating the blended mixture using a lubricant;
 - granulating the lubricated blend;
 - lubricating the resultant granulation using the lubricant; and
 - compressing the lubricated granulation into desired form.

14. The process of claim 13, wherein the pharmaceutically acceptable salt of omecamtiv mecarbil or pharmaceutically acceptable hydrate thereof is omecamtiv mecarbil dihydrochloride hydrate.
15. Use of a pharmaceutical formulation according to any one of Claims 1-12 in the manufacture of a medicament for treating a disease selected from acute heart failure and chronic heart failure.
16. A pharmaceutical formulation according to any one of Claims 1-12, wherein the administration of the formulation to a human results in exposure to omecamtiv mecarbil from two to twelve hours after administration of between 40 and 70 ng/ml.
17. The pharmaceutical formulation according to Claim 16, wherein the exposure from two to twelve hours after administration is between 40 and 55 ng/ml.
18. The pharmaceutical formulation according to Claim 16 or 17, wherein the administration is oral administration.
19. A pharmaceutical formulation according to any one of Claims 1-12, wherein omecamtiv mecarbil is released in the following intervals:
 - $\leq 30\%$ dose dissolved at 1 hour;
 - 30-75% dose dissolved at 3 hours; and
 - $\geq 80\%$ dose dissolved at 12 hours.
20. A pharmaceutical formulation according to any one of Claims 1-12, wherein omecamtiv mecarbil is released in the following intervals:
 - $\leq 30\%$ dose dissolved at 2 hours;
 - 30-75% dose dissolved at 6 hours; and
 - $\geq 80\%$ dose dissolved at 16 hours.
21. The pharmaceutical formulation according to Claim 1, having a weight ratio of the pH-modifying agent to the pharmaceutically acceptable salt of omecamtiv mecarbil, or pharmaceutically acceptable hydrate thereof, of less than 2:1 to 1:1.

22. The pharmaceutical formulation according to Claim 21, having a weight ratio of the pH-modifying agent to the pharmaceutically acceptable salt of omecamtiv mecarbil, or pharmaceutically acceptable hydrate thereof, of 1:1.
23. The pharmaceutical formulation according to Claim 1, comprising:
- 5-7% w/w omecamtiv mecarbil dihydrochloride hydrate;
 - 27-33% w/w control release agent;
 - 52-58% w/w filler;
 - 6-9% w/w fumaric acid; and
 - 0.2-2% w/w lubricant.
24. The pharmaceutical formulation according to Claim 23, wherein the control release agent comprises hypromellose having a viscosity of 100,000 mPa.s at 2% concentration in water at 20°C.
25. The pharmaceutical formulation according to Claim 23, wherein the control release agent comprises hypromellose having a viscosity of 100 mPa.s at 2% concentration in water at 20°C.
26. The pharmaceutical formulation according to Claim 23, wherein the filler comprises microcrystalline cellulose.
27. The pharmaceutical formulation according to Claim 23, wherein the filler comprises lactose monohydrate.
28. The pharmaceutical formulation according to Claim 1, comprising:
- 17-20% w/w omecamtiv mecarbil dihydrochloride hydrate;
 - 21-29% w/w control release agent;
 - 34-41% w/w filler;
 - 17-20% w/w fumaric acid; and
 - 0.2-2% w/w lubricant.
29. The pharmaceutical formulation according to Claim 28, wherein the control release agent comprises hypromellose having a viscosity of 100,000 mPa.s at 2% concentration in water at 20°C.

30. The pharmaceutical formulation according to Claim 28, wherein the control release agent comprises hypromellose having a viscosity of 100 mPa.s at 2% concentration in water at 20°C.
31. The pharmaceutical formulation according to Claim 28, wherein the filler comprises microcrystalline cellulose.
32. The pharmaceutical formulation according to Claim 28, wherein the filler comprises lactose monohydrate.
33. The pharmaceutical formulation according to Claim 1, comprising:
12-25% w/w omecamtiv mecarbil dihydrochloride hydrate;
25-35% w/w control release agent;
25-40% w/w filler;
12-25% w/w fumaric acid; and
0.2-4% w/w lubricant.
34. The pharmaceutical formulation according to Claim 1, comprising:
3-10% w/w omecamtiv mecarbil dihydrochloride hydrate;
20-40% w/w control release agent;
42-67% w/w filler;
4-11% w/w fumaric acid; and
0.2-4% w/w lubricant.
35. The pharmaceutical formulation according to Claim 1, comprising:
12-25% w/w omecamtiv mecarbil dihydrochloride hydrate;
13-37% w/w control release agent;
24-50% w/w filler;
12-25% w/w fumaric acid; and
0.2-4% w/w lubricant.