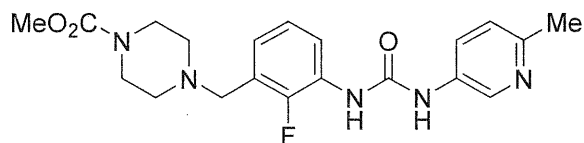


[0005] U.S. Patent No. 7,507,735, herein incorporated by reference, discloses a genus of compounds, including omecamtiv mecarbil (AMG 423, CK-1827452), having the structure:



[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:

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

a control release agent;

a pH modifying agent selected from the group consisting of maleic acid, fumaric acid, sulfuric acid, tartaric acid, lactic acid, salicylic acid, aspartic acid, aminosalicic acid, malonic 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 ~~omecamtiv mecarbil, or a pharmaceutically acceptable salt of omecamtiv mecarbil, a pharmaceutically acceptable hydrate, or a pharmaceutically acceptable hydrate of a pharmaceutically acceptable salt thereof,~~ a control release agent, a pH modifying agent, and a filler;

lubricating the blended mixture using a lubricant;

granulating the lubricated blend;

What is Claimed:

1. A pharmaceutical formulation comprising:
omecamtiv mecarbil, or a pharmaceutically acceptable salt, a pharmaceutically acceptable hydrate, or a pharmaceutically acceptable hydrate of a pharmaceutically acceptable salt thereof;
a control release agent;
a pH modifying agent;
a filler; and
a lubricant.
2. The pharmaceutical formulation of claim 1, wherein the omeclamtiv mecarbil is present as omeclamtiv mecarbil dihydrochloride hydrate.
3. A pharmaceutical formulation according to Claim 1 or 2, wherein the pH modifying agent is selected from maleic acid, citric acid, tartaric acid, pamoic acid, fumaric acid, salicylic acid, 2,6-diaminohexanoic acid, camphorsulfonic acid, glycerophosphoric acid, 2-hydroxyethanesulfonic acid, isethionic acid, succinic acid, carbonic acid, p-toluenesulfonic acid, aspartic acid, 8-chlorotheophylline, benzenesulfonic acid, malic acid, orotic acid, oxalic acid, benzoic acid, 2-naphthalenesulfonic acid, stearic acid, adipic acid, p-amino-salicylic acid, 5-aminosalicylic acid, ascorbic acid, sulfuric acid, cyclamic acid, sodium lauryl sulfate, glucoheptonic acid, glucuronic acid, glycine, sulfuric acid, mandelic acid, 1,5-naphthalenedisulfonic acid, nicotinic acid, oleic acid, 2-oxoglutaric acid, pyridoxal 5-phosphate, undecanoic acid, p-acetamidobenzoic acid, o-acetamidobenzoic acid, m-acetamidobenzoic acid, N-acetyl-L-aspartic acid, camphoric acid, dehydrocholic acid, malonic acid, edetic acid, ethylenediaminetetraacetic acid, ethylsulfuric acid, hydroxyphenylbenzoylbenzoic acid, glutamic acid, glycyrrhizic acid, 4-hexylresorcinol, hippuric acid, p-phenolsulfonic acid, 4-hydroxybenzoic acid, 3-hydroxybenzoic acid, 3-hydroxy-2-naphthoic acid, 1-hydroxy-2-naphthoic acid, lactobionic acid, 3'-adenylic acid, 5'-adenylic acid, mucic acid, galactaric acid, pantothenic acid, pectic acid, polygalacturonic acid, 5-sulfosalicylic acid, 1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopurine-7-propanesulfonic acid, terephthalic acid, 1-hydroxy-2-naphthoic acid, and any combination thereof.

4. A pharmaceutical formulation according to Claim 3, wherein the pH modifying agent is selected from maleic acid, citric acid, malic acid, fumaric acid, sulfuric acid, tartaric acid, lactic acid, salicylic acid, aspartic acid, aminosalicic acid, malonic acid, glutamic acid, and any combination thereof.
5. A pharmaceutical formulation according to Claim 4, wherein the pH modifying agent is fumaric acid.
6. A pharmaceutical formulation according to any one of Claims 1-5, wherein the filler is selected from starches, lactose, mannitol, cellulose derivatives, calcium phosphate, a sugar, and any combination thereof.
7. A pharmaceutical formulation according to any one of Claims 1-6, wherein the control release agent is MethocelTM K100 M Prem CR.
8. A pharmaceutical formulation according to any one of Claims 1-6, wherein the control release agent is MethocelTM K100 LV Prem CR.
9. A pharmaceutical formulation according to any one of Claims 1-6, wherein the control release agent is a mixture of MethocelTM K100 M Prem CR and MethocelTM K100 LV Prem CR.
10. A pharmaceutical formulation according to any one of Claims 1-9, wherein the filler is a combination of microcrystalline cellulose and lactose monohydrate.
11. A pharmaceutical formulation according to any one of Claims 1-10, wherein the lubricant is magnesium stearate.
12. A pharmaceutical formulation according to any one of Claims 1-11, wherein the formulation is in the form of a tablet.
13. The pharmaceutical formulation according to any one of Claims 1-12 comprising: 3-30% w/w of omecamtiv mecarbil, or a pharmaceutically acceptable salt, a

pharmaceutically acceptable hydrate, or a pharmaceutically acceptable hydrate of a pharmaceutically acceptable salt 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.

14. A process for making a pharmaceutical formulation according to Claim 1, comprising: blending a mixture comprising omecamtiv mecarbil, or a pharmaceutically acceptable salt, a pharmaceutically acceptable hydrate, or a pharmaceutically acceptable hydrate of a pharmaceutically acceptable salt 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.

15. The process of claim 14, wherein the omecamtiv mecarbil is present as omecamtiv mecarbil dihydrochloride hydrate.

16. A pharmaceutical formulation prepared by the process of claim 14 or 15.

17. Use of a pharmaceutical formulation according to any one of Claims 1-13 or 16 in the manufacture of a medicament for treating a disease selected from acute heart failure and chronic heart failure.

18. A pharmaceutical formulation according to any one of Claims 1-13, wherein the exposure of omecamtiv mecarbil from two to twelve hours after dosing in humans remains between 40 and 70 ng/ml.

19. The pharmaceutical composition according to Claim 18, wherein the exposure of omecamtiv mecarbil from two to twelve hours after dosing in humans remains between 40 and 55 ng/ml.

20. A pharmaceutical composition according to any one of Claims 1-13, wherein the 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.

21. A pharmaceutical composition according to any one of Claims 1-13, wherein the 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.

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, sulfuric acid, tartaric acid, lactic acid, salicylic acid, aspartic acid, aminosalicic acid, malonic 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 selected from maleic acid, fumaric acid, tartaric acid, glutamic acid, and any combination thereof.
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.