TITLE

PHARMACEUTICAL COMPOSITION COMPRISING OMEGA-3 FATTY ACID AND HYDROXY-DERIVATIVE OF A STATIN AND METHODS OF USING SAME

BACKGROUND

[0001] Cardiovascular disease is one of the leading causes of death in the United States and most European countries. It is estimated that over 70 million people in the United States alone suffer from a cardiovascular disease or disorder including but not limited to high blood pressure, coronary heart disease, dislipidemia, congestive heart failure and stroke. A need exists for improved treatments for cardiovascular-related diseases and disorders.

SUMMARY

[0002] In various ~~embodiments~~examples, the present ~~invention provides~~ disclosure describes pharmaceutical compositions and methods of using such compositions to treat and/or prevent cardiovascular-related diseases. In one ~~embodiment~~example, a pharmaceutical composition comprising a statin or derivative of a statin, for example a hydroxy-derivative of a statin, or a pharmaceutically acceptable salt thereof and an omega-3 fatty acid and is provided. The term "hydroxy-derivative of a statin" herein refers to a parent statin compound (i.e. known class of HMG-CoA reductase inhibitors) having at least one hydroxy substituent group. In one ~~embodiment~~example, a hydroxyl group is attached to a phenyl ring of the parent statin. In one aspect, the present invention refers to pharmaceutical composition comprising (a) a hydroxy-derivative of atorvastatin or pharmaceutically acceptable salt thereof and (b) an oil comprising eicosapentaenoic acid or derivative thereof.

[0003] In another ~~embodiment~~example, a pharmaceutical composition comprising a hydroxy-derivative of a statin or a pharmaceutically acceptable salt thereof and an oil comprising an omega-3 fatty acid is provided. In a related ~~embodiment~~example, the oil comprises at least 95% by weight eicosapentaenoic acid or derivative thereof, for example ethyl eicosapentaenoate.

[0004] In various ~~embodiments~~examples, the hydroxy-derivative of a statin is selected from a hydroxy-derivative of atorvastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, fluvastatin, simvastatin, lovastatin, cerivastatin and pharmaceutically acceptable salts thereof.

[0005] In other ~~embodiments~~examples, the hydroxy-derivative of a statin is selected from ortho or para hydroxy-atorvastatin, p-hydroxy atorvastatin calcium, p-hydroxy atorvastatin disodium, o-hydroxy atorvastatin calcium, o-hydroxy atorvastatin lactone, o-hydroxy atorvastatin-d5 calcium, o-hydroxy atorvastatin-d5 disodium, o-hydroxy atorvastatin-d5 lactone, 2-hydroxy atorvastatin bisodium, p-hydroxy atorvastatin lactone, p-hydroxy

atorvastatin-d5 calcium, p-hydroxy atorvastatin-d5 lactone, and 4-hydroxy atorvastatin bisodium.

[0006] In still other ~~embodiments~~examples, the oil comprises one or more of: (a) about 0.2% to about 0.5%) by weight ethyl octadecatetraenoate, (b) about 0.05% to about 0.20%o by weight ethyl nonaecapentaenoate, (c) about 0.2% to about 3% by weight ethyl arachidonate, (d) about 0.3% to about 0.5% by weight ethyl eicosatetraenoate, (e) about 0.8% to about 0.25% by weight ethyl heneicosapentaenoate, (f) about 0.02% to about 0.1% by weight ethyl 17E-icosapentaenoate, (g) about 0.02% to about 0.1% by weight ethyl 5-icosapentanoate, (h) about 0.01% to about 0.15% by weight ethyl 5E,8E-icosapentaenoate, (i) about 0.01% to about 0.15% by weight ethyl 8E, 11E-icosapentaenoate, (j) about 0.01% to about 0.15% by weight ethyl 5E, 14E-icosapentaenoate, (k) about 0.01% to about 0.15% by weight ethyl 5E, 8E, 11E, 17E-icosapentaenoate, (l) no amount or substantially no amount of ethyl icosahexaenoate, (m) no amount or substantially no amount of ethyl 11Z-eicosenoate, (n) no amount or substantially no amount of ethyl docosahexaenoic acid, and/or (o) about 0.02% to about 0.1% ethyl nonadecapentaenoate.

[0007] In one aspect, the present invention refers to use of a hydroxy-derivative of atorvastatin or pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a cardiovascular-related disease, wherein the medicament further comprises an oil comprising eicosapentaenoic acid or derivative thereof. In yet another ~~embodiment~~example, the ~~invention provides~~disclosure describes a method of treating a cardiovascular-related disease in a subject in need thereof comprising administering a composition as described herein to the subject. In one ~~embodiment~~example, the cardiovascular-related disease is artherosclerosis.

[0008] These and other embodiments of the present invention will be disclosed in further detail herein below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] Fig. 1 shows effects of EPA, DHA and EPA/DHA, in combination with atorvastatin, atorvastatin *o*-hydroxy metabolite, simvastatin or rosuvastatin, on membrane lipid peroxidation.

[0010] Fig. 2 shows effects of EPA in combination with atorvastatin, atorvastatin *o*-hydroxy metabolite, simvastatin or rosuvastatin, on membrane lipid peroxidation.

[0011] Fig. 3 shows effects of DHA in combination with atorvastatin, atorvastatin *o*-hydroxy metabolite, simvastatin or rosuvastatin, on membrane lipid peroxidation.

[0012] Fig. 4 shows effects of EPA/DHA in combination with atorvastatin, atorvastatin *o*-hydroxy metabolite, simvastatin or rosuvastatin, on membrane lipid peroxidation.

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising (a) a hydroxy-derivative of a statin or pharmaceutically acceptable salt thereof and (b) an oil comprising an omega-3 fatty acid.

2. The pharmaceutical composition of claim 1 wherein the omega-3 fatty acid comprises ethyl eicosapentaenoate.

3. The pharmaceutical composition of claim 1 wherein the oil comprises at least 95% by weight ethyl eicosapentaenoate.

4. The pharmaceutical composition of claim 1 wherein the oil comprises at least 95% by weight ethyl docosahexaenoic acid.

5. The pharmaceutical composition of claim 3 wherein the oil comprises ethyl eicosapentaenoate and ethyl docosahexaenoic acid.

6. The pharmaceutical composition of claim 5 wherein the oil comprises ethyl eicosapentaenoate and ethyl docosahexaenoic acid in a mole ratio of about 1:1 to about 1.5:1.

7. The pharmaceutical composition of claim 1 wherein the hydroxy-derivative of a statin or pharmaceutically acceptable salt thereof is selected from a hydroxy-derivative of atorvastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, fluvastatin, simvastatin, lovastatin, cerivastatin and pharmaceutically acceptable salts thereof.

8. The pharmaceutical composition of claim 7 wherein the hydroxy-derivative of a statin is selected from ortho or para hydroxy-atorvastatin and pharmaceutically acceptable salts thereof.

9. The pharmaceutical composition of claim 8 wherein the hydroxy-derivative of a statin or pharmaceutically acceptable salt thereof is selected from o-hydroxy atorvastatin, p-hydroxy atorvastatin, p-hydroxy atorvastatin calcium, p-hydroxy atorvastatin disodium, o-

hydroxy atorvastatin calcium, o-hydroxy atorvastatin lactone, o-hydroxy atorvastatin-d5 calcium, o-hydroxy atorvastatin-d5 disodium, o-hydroxy atorvastatin-d5 lactone, 2-hydroxy atorvastatin bisodium, p-hydroxy atorvastatin lactone, p-hydroxy atorvastatin-d5 calcium, p-hydroxy atorvastatin-d5 lactone, and 4-hydroxy atorvastatin bisodium.

10. The pharmaceutical composition of claim 1 further comprising tocopherol in an amount of about 0.1% to about 0.3%, by weight.

11. The pharmaceutical composition of claim 1 wherein about 0.5 g to about 2 g of said composition is present in a capsule shell.

12. A method of treating a cardiovascular-related disease in a subject in need thereof comprising administering to the subject a composition comprising (a) a hydroxy-derivative of a statin or pharmaceutically acceptable salt thereof and (b) an oil comprising an omega-3 fatty acid.

13. The method of claim 12 wherein the omega-3 fatty acid comprises ethyl eicosapentaenoate.

14. The method of claim 13 wherein the oil comprises at least 95% by weight ethyl eicosapentaenoate.

15. The method of claim 14 wherein the oil comprises ethyl eicosapentaenoate and ethyl docosahexaenoic acid in a mole ratio of about 1.1 to 1 to about 1.5 to 1.

16. The method of claim 14 wherein the oil comprises ethyl docosahexaenoic acid.

17. The method of claim 12 wherein the hydroxy-derivative of a statin or pharmaceutically acceptable salt thereof is selected from ortho or para hydroxy atorvastatin and pharmaceutically acceptable salts thereof.

18. The method of claim 12 wherein the hydroxy-derivative of a statin or pharmaceutically acceptable salt thereof is selected from o-hydroxy atorvastatin, p-hydroxy atorvastatin, p-hydroxy atorvastatin calcium, p-hydroxy atorvastatin disodium, o-hydroxy atorvastatin calcium, o-hydroxy atorvastatin lactone, o-hydroxy atorvastatin-d5 calcium, o-hydroxy atorvastatin-d5 disodium, o-hydroxy atorvastatin-d5 lactone, 2-hydroxy atorvastatin bisodium, p-hydroxy atorvastatin lactone, p-hydroxy atorvastatin-d5 calcium, p-hydroxy atorvastatin-d5 lactone, and 4-hydroxy atorvastatin bisodium.

19. The method of claim 12 wherein the cardiovascular disease is selected from hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia, coronary heart disease, vascular disease, stroke, atherosclerosis, arrhythmia, hypertension, and myocardial infarction.

20. The method of claim 12 wherein the cardiovascular disease is atherosclerosis.

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising (a) a hydroxy-derivative of atorvastatin or pharmaceutically acceptable salt thereof and (b) an oil comprising eicosapentaenoic acid or derivative thereof.

2. The pharmaceutical composition of claim 1 wherein the eicosapentaenoic acid or derivative thereof comprises ethyl eicosapentaenoate.

3. The pharmaceutical composition of claim 2 wherein the oil comprises at least 95% by weight of the ethyl eicosapentaenoate.

4. The pharmaceutical composition of claim 1 wherein the oil comprises eicosapentaenoic acid in free acid form.

5. The pharmaceutical composition of claim 4 wherein the oil comprises at least 95% by weight of the eicosapentaenoic acid in free acid form.

6. The pharmaceutical composition of claim 1 wherein the hydroxy-derivative of atorvastatin is selected from ortho or para hydroxy-atorvastatin and pharmaceutically acceptable salts thereof.

7. The pharmaceutical composition of claim 6 wherein the hydroxy-derivative of atorvastatin or pharmaceutically acceptable salt thereof is selected from o-hydroxy atorvastatin, p-hydroxy atorvastatin, p-hydroxy atorvastatin calcium, p-hydroxy atorvastatin disodium, o-hydroxy atorvastatin calcium, o-hydroxy atorvastatin lactone, o-hydroxy atorvastatin-d5 calcium, o-hydroxy atorvastatin-d5 disodium, o-hydroxy atorvastatin-d5 lactone, 2-hydroxy atorvastatin bisodium, p-hydroxy atorvastatin lactone, p-hydroxy atorvastatin-d5 calcium, p-hydroxy atorvastatin-d5 lactone, and 4-hydroxy atorvastatin bisodium.

8. The pharmaceutical composition of claim 1 further comprising tocopherol in an amount of about 0.1% to about 0.3%, by weight.

9. The pharmaceutical composition of claim 1 wherein about 0.5 g to about 2 g of said composition is present in a capsule shell.

10. Use of a hydroxy-derivative of atorvastatin or pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a cardiovascular-related disease, wherein the medicament further comprises an oil comprising eicosapentaenoic acid or derivative thereof.

11. The use of claim 10 wherein the eicosapentaenoic acid or derivative thereof comprises ethyl eicosapentaenoate.

12. The use of claim 11 wherein the oil comprises at least 95% by weight of the ethyl eicosapentaenoate.

13. The use of claim 10 wherein the oil comprises eicosapentaenoic acid in free acid form.

14. The use of claim 13 wherein the oil comprises at least 95% by weight of the eicosapentaenoic acid in free acid form.

15. The use of claim 10 wherein the hydroxy-derivative of atorvastatin or pharmaceutically acceptable salt thereof is selected from ortho or para hydroxy atorvastatin and pharmaceutically acceptable salts thereof.

16. The method of claim 10 wherein the hydroxy-derivative of a statin or pharmaceutically acceptable salt thereof is selected from o-hydroxy atorvastatin, p-hydroxy atorvastatin, p-hydroxy atorvastatin calcium, p-hydroxy atorvastatin disodium, o-hydroxy atorvastatin calcium, o-hydroxy atorvastatin lactone, o-hydroxy atorvastatin-d5 calcium, o-hydroxy atorvastatin-d5 disodium, o-hydroxy atorvastatin-d5 lactone, 2-hydroxy atorvastatin bisodium p-hydroxy atorvastatin lactone, p-hydroxy atorvastatin-d5 calcium, p-hydroxy atorvastatin-d5 lactone, and 4-hydroxy atorvastatin bisodium.

17. The use of claim 10 wherein the cardiovascular disease is selected from hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia, coronary heart disease, vascular disease, stroke, atherosclerosis, arrhythmia, hypertension, and myocardial infarction.

18. The use of claim 10 wherein the cardiovascular disease is atherosclerosis.