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~~disclosure provides 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.

[0002a] In one aspect, there is provided 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, the omega-3 fatty acid comprising at least 95%, by weight, ethyl eicosapentaenoate or at least 95%, by weight, ethyl docosahexaenoate.

[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, 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% 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 yet another ~~embodiment~~example, the ~~invention~~present disclosure provides 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.

[0007a] In yet another aspect, there is provided the use of 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 in the manufacture of a medicament for the treatment of a cardiovascular-related disease in a subject in need thereof, the omega-3 fatty acid comprising at least 95%, by weight, ethyl eicosapentaenoate or at least 95%, by weight, ethyl docosahexaenoate.

[0008] These and other ~~embodiments~~examples of the present ~~invention~~disclosure 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.