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(54) **COMPOSITIONS FOR LOWERING SERUM CHOLESTEROL AND/OR TRIGLYCERIDES**

(76) Inventor: **Gerald L. Wisler**, Gladstone, NJ (US)

Correspondence Address:
GOODWIN PROCTER LLP
PATENT ADMINISTRATOR
EXCHANGE PLACE
BOSTON, MA 02109-2881 (US)

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(57) **ABSTRACT**

The invention provides methods and compositions for treating hyperlipidemia and disorders associated with hyperlipidemia in a mammal. Compositions useful in the practice of the invention include a microsomal triglyceride transport protein inhibitor ("MTPI") and at least two other cholesterol lowering drugs selected from the group consisting of a cholesterol absorption inhibitor ("CAI"), a HMG-CoA reductase inhibitor, a bile acid sequestrant, a fibric acid derivative, niacin, and squalene synthetase inhibitor.

COMPOSITIONS FOR LOWERING SERUM CHOLESTEROL AND/OR TRIGLYCERIDES

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application Ser. No. 60/788,616, filed Apr. 3, 2006, and U.S. Provisional Patent Application Ser. No. 60/727,664, filed Oct. 18, 2005, the entire disclosures of which are incorporated by reference herein.

FIELD OF THE INVENTION

[0002] The present invention relates generally to the field of pharmaceutical compositions and their use in the treatment of hyperlipidemia, and more particularly relates to therapeutic combinations comprising a microsomal triglyceride transfer protein inhibitor and at least two other cholesterol lowering agents, and their use in the treatment of hyperlipidemia.

BACKGROUND OF THE INVENTION

[0003] There are several known risk factors for atherosclerotic cardiovascular disease (ASCVD), the major cause of mortality in the Western world. One key risk factor is hyperlipidemia, which is the presence of elevated levels of lipids in blood plasma. Various epidemiological studies have demonstrated that drug mediated lowering of total cholesterol (TC) and low density lipoprotein (LDL) cholesterol (LDL-C) is associated with a significant reduction in cardiovascular events. The National Cholesterol Education Program's (NCEP's) updated guidelines recommends that the overall goal for high-risk patients is to achieve less than 100 mg/dL of LDL, with a therapeutic option to set the goal for such patients to achieve a LDL level less than 70 mg/dL.

[0004] One form of hyperlipidemia is known as hypertriglyceridemia and results in the presence of elevated amounts of triglycerides in the blood. Although triglycerides are necessary for good health, higher-than-normal triglyceride levels, often are associated with known risk factors for heart disease.

[0005] Another form of hyperlipidemia, known as hypercholesterolemia, which is the presence of elevated amounts of cholesterol in the blood, is a polygenic disorder. Modifications in lifestyle and conventional drug treatment are usually successful in reducing cholesterol levels. However, in some cases, as in familial hypercholesterolemia (FH), the cause is a monogenic defect. Treatment of a patient with FH can be more challenging because the levels of LDL-C remain elevated despite aggressive use of conventional therapy.

[0006] For example, one type of FH, homozygous familial hypercholesterolemia (hoFH), is a serious life-threatening genetic disease caused by homozygosity or compound heterozygosity for mutations in the low density lipoprotein (LDL) receptor. Patients with hoFH typically have total plasma cholesterol levels over 400 mg/dL resulting in premature atherosclerotic vascular disease. When left untreated, most patients develop atherosclerosis before age 20 and generally do not survive past age 30. However, patients diagnosed with hoFH are largely unresponsive to conventional drug therapy and have limited treatment options. Specifically, treatment with statins, which reduce LDL-C by inhibiting cholesterol synthesis and upregulating the hepatic LDL receptor, have negligible effect in patients whose LDL receptors are non-existent or defective. A mean LDL-C reduction maximal dose of statins (atorvastatin or simvastatin administered at 80 mg/day). The addition of ezetimibe 10 mg/day to this regimen resulted in a total reduction of LDL-C levels of 27%, which is still far from optimal. Non-pharmacological options have also been tested, including surgical interventions, such as portacaval shunt and ileal bypass, and orthotopic liver transplantation, but with clear disadvantages and risks. Therefore, there is a tremendous unmet medical need for new medical therapies for hoFH.

[0007] Microsomal triglyceride transfer protein (MTP) inhibitors have been developed as potent inhibitors of MTP-mediated neutral lipid transfer activity. MTP catalyzes the transport of triglyceride, cholesteryl ester, and phosphatidylcholine between small unilamellar vesicles. One exemplary MTP inhibitor is BMS-201038, developed by Bristol-Myers Squibb. See, U.S. Pat. Nos. 5,739,135; and 5,712,279. Studies using an animal model for homozygous FH indicated that BMS-201038 effectively reduced plasma cholesterol levels in a dose dependent manner, for example, at 25 mg/day, suggesting that this compound might be effective for treating patients with hoFH. It was noticed, however, that certain patients treated with 25 mg/day of BMS-201038 experienced certain adverse events, for example, gastrointestinal disturbances, abnormalities in liver function, and hepatic steatosis. Although a promising therapeutic agent, large scale clinical trials of BMS-201038 have been discontinued. Another potent MIP inhibitor known as implitapide has been developed. See, U.S. Pat. Nos. 6,265,431, 6,479,503, 5,952,498. During clinical studies, dosages of implitapide of 80 mg/day or greater, although therapeutically effective, were found to result in certain adverse events, for example, gastrointestinal disturbances, abnormalities in liver function, and hepatic steatosis. Large scale clinical studies using implitapide have also been discontinued.

[0008] Accordingly, there is still a need for methods for aggressively treating hyperlipidemias that effectively lower, for example, circulating cholesterol and triglycerides levels so as to improve the rates of achieving goals of therapy based on published guidelines, for example, NCEP guidelines, but with fewer or reduced adverse effects that typically result when higher dosages of the MTP inhibitor are used alone in monotherapy.

BRIEF SUMMARY OF THE INVENTION

[0009] The invention is based, in part, upon the development of compositions comprising an MTP inhibitor in combination with at least two other cholesterol lowering agents. It is contemplated that the combination of active ingredients will not only provide a greater degree of goal attainment, but it will also permit the goals to be achieved at lower dosages of the individual active ingredients thereby reducing the incidence and/or severity of dose-related adverse events associated with the individual active ingredients. It is contemplated that, for example, lowering blood LDL levels below those already achieved in earlier clinical trials by using, for example, an MTP inhibitor in combination with a HMG-CoA reductase inhibitor plus a cholesterol absorption inhibitor (CAI) will provide further improvements in cardiovascular event rate reduction and/or plaque regression.

[0010] For example, the compositions can be used to reduce the fasting levels of cholesterol and/or triglycerides in the blood of a mammal to meet a clinical endpoint but with

sufficient to meet the clinical endpoint or (ii) when the MTP inhibitor is administered together with another cholesterol lowering agent, where the MTP inhibitor and the other cholesterol lowering agent are administered at dosages sufficient to meet the clinical end point.

[0011] Furthermore, the compositions can be used to reduce by at least 55%, 60%, or 65%, the blood LDL concentration in a population of patients who, prior to therapy have circulating LDL concentrations of at least 130 mg/dL, so as to meet the goal of having an LDL concentration of 70 mg/dL or less, where (i) less than 2% of the patients in the population have Liver Function Test results three times greater than the upper limit of normal of a standard clinical laboratory range or (ii) the patients have statistically significant lower rates of skeletal muscle side effects (e.g., myalgia and/or myopathy) relative to patients receiving the maximum permitted dose of a HMG-CoA reductase inhibitor. In this context, the term "permitted" refers to a maximum dosage permitted by a regulatory agency, for example, the U.S. Food and Drug Agency.

[0012] Furthermore, it is contemplated that the compositions, when administered to the recipient, will not only permit the recipient to meet a cholesterol goal but will also slow down or stop the build up of plaques, for example, atherosclerotic plaques, on the walls of blood vessels. Under certain circumstances, it is contemplated that the compositions, when administered, will also induce regression of existing plaques.

[0013] In one aspect, the invention provides a pharmaceutical composition comprising (i) a MTP inhibitor, (ii) a CAI, and (iii) at least one cholesterol lowering drug selected from the group consisting of a HMG-CoA reductase inhibitor, a bile acid sequestrant, a fibric acid derivative, niacin, and a squalene sythetase inhibitor. In another aspect, the invention provides a pharmaceutical composition comprising (i) an MTPI, (ii) a HMG-CoA reductase inhibitor, and (iii) at least one cholesterol lowering drug selected from the group consisting of a bile acid sequestrant, a fibric acid derivative, niacin, and a squalene sythetase inhibitor.

[0014] It is possible that the pharmaceutical composition can comprise an MTPI, (ii) a CAI, (iii) a HMG-CoA reductase inhibitor, and (iv) a cholesterol lowering drug selected from the group consisting of a bile acid sequestrant, a fibric acid derivative, and niacin.

[0015] The MTPI can be selected from known compounds selected from the group consisting of BMS-201038, implitapide, JTT-130 and CP-346086, and SLx-4090. The HMG-CoA reductase inhibitor can be selected from the group consisting of mevastatin, lovastatin, pravastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, tenivastatin, rosuvastatin, pitavastatin. The CAI can be selected from the group consisting of ezetimibe or a derivative thereof, MD-0727, FM-VP4, LPD-179, LPD84, and LPD145. The bile acid sequestrant can be selected from the group consisting of cholestyramine, colesevelam and colestipol. The fibric acid derivative can be selected from the group consisting of fenofibrate, bezafibrate, ciprofibrate, clofibrate, and gemfibrozil.

DETAILED DESCRIPTION OF THE INVENTION

(1) Definitions

[0016] For convenience, certain terms used in the specification, examples, and appended claims are collected here.

other cholesterol lowering agents, for example, where one is a HMG Co-A reductase and the other is a CAI, as part of a specific treatment regimen intended to provide the beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually weeks, months or years depending upon the combination selected). Combination therapy is intended to embrace administration of multiple therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single tablet or capsule having a fixed ratio of each therapeutic agent or in multiple, single capsules for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection.

[0018] Combination therapy also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients and non-drug therapies. Where the combination therapy further comprises a non-drug treatment, the non-drug treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and non-drug treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the non-drug treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

[0019] The components of the combination may be administered to a patient simultaneously or sequentially. It will be appreciated that the components may be present in the same pharmaceutically acceptable carrier and, therefore, are administered simultaneously. Alternatively, the active ingredients may be present in separate pharmaceutical carriers, such as, conventional oral dosage forms, that can be administered either simultaneously or sequentially.

[0020] The terms, "individual," "patient," or "subject" are used interchangeably herein and include any mammal, including animals, for example, primates, for example, humans, and other animals, for example, dogs, cats, swine, cattle, sheep, and horses. The compounds of the invention can be administered to a mammal, such as a human, but can also be other mammals, for example, an animal in need of veterinary treatment, for example, domestic animals (for example, dogs, cats, and the like), farm animals (for example, cows, sheep, pigs, horses, and the like) and laboratory animals (for example, rats, mice, guinea pigs, and the like).

statin monotherapy has been found ineffective or less effective than desired. A physician designing lipid reduction therapy for a patient will be able to determine via diagnosis and observation of periodic blood cholesterol and/or triglyceride levels whether such a patient is or has been resistant to statin monotherapy.

[0022] The term, "statin-intolerant patient," as used herein includes those patients for whom conventional statin therapy, for example, for serum lipid reduction, has been found to be ineffective and/or for whom an effective lipid-reducing dose of statins is too high to be tolerated or that there is an unacceptable adverse event associated with a particular dose. For example, statin therapy may be discontinued by the physician/patient due to concern over an adverse event such as Liver Function Test abnormality, muscle aches and pains or inflammation—myalgia or myostitis, elevation in enzymes (CK) showing muscle adverse event. A physician designing lipid reduction therapy for a patient will be able to determine via diagnosis and observation of periodic blood cholesterol and/or triglyceride levels whether such a patient is statin-intolerant.

[0023] The phrase "minimizing adverse effects," "reducing adverse events," or "reduced adverse events," as used herein refer to an amelioration or elimination of one or more undesired side effects associated with the use of MTP inhibitors of the present invention. Side effects of traditional use of the MTP inhibitors include, without limitation, nausea, gastrointestinal disorders, steatorrhea, abdominal cramping, distention, elevated liver function tests, fatty liver (hepatic steatosis); hepatic fat build up, polyneuropathy, peripheral neuropathy, rhabdomyolysis, arthralgia, myalgia, chest pain, rhinitis, dizziness, arthritis, peripheral edema, gastroenteritis, liver function tests abnormal, colitis, rectal hemorrhage, esophagitis, eructation, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice, paresthesia, amnesia, libido decreased, emotional lability, incoordination, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia, leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia, anaphylaxis, angioneurotic edema, and bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis). Accordingly, the methods described herein provide an effective therapy while at the same time causing fewer or less significant adverse events.

[0024] In certain embodiments, side effects are partially eliminated. As used herein, the phrase "partially eliminated" refers to a reduction in the severity, extent, or duration of the particular side effect by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% and 99% relative to that found by administering 25 mg/day of BMS-201038 during monotherapy or either 80 mg/day or 160 mg/day of implitapide during monotherapy. In certain embodiments, side effects are completely eliminated. Those skilled in the art are credited with the ability to detect and grade the severity, extent, or duration of side effects as well as the degree of amelioration of a side effect. In some embodiments, two or more side effects are ameliorated.

[0025] The term, "therapeutically effective" refers to the ability of an active ingredient, for example, BMS-201038 and

other clinician. Non-limiting examples include reduction of cholesterol (for example, LDL-C) and/or triglyceride levels in a patient, reduction of the amount of plaques, for example, arterial plaques, on the wall of a blood vessel, and the like.

[0026] The term, "therapeutically effective amount" includes the amount of an active ingredient, for example, BMS-201038 and implitapide, that will elicit the biological or medical response that is being sought by the researcher, veterinarian, medical doctor or other clinician. The compounds of the invention are administered in amounts effective at lowering the cholesterol concentration in the blood, and/or the triglyceride concentration in the blood and/or reducing the amount of plaques, for example, arterial plaques disposed upon the blood contacting wall of one or more blood vessels. Alternatively, a therapeutically effective amount of an active ingredient is the quantity of the compound required to achieve a desired therapeutic and/or prophylactic effect, such as the amount of the active ingredient that results in the prevention of or a decrease in the symptoms associated with the condition (for example, to meet an end-point).

[0027] The terms, "pharmaceutically acceptable" or "pharmacologically acceptable" refer to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or to a human, as appropriate. The term, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

[0028] The terms "treating" or "treatment", refers to any effect, for example, lessening, inhibiting, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, or disorder.

(2) Formulations for Combination Therapy

[0029] The compositions provided herein are useful for treating a number of disorders associated with elevated levels of cholesterol and/or triglycerides in the blood. The compositions comprise an MTP inhibitor in combination with at least two other cholesterol lowering drugs.

[0030] In one aspect, the composition comprises (i) an MTP inhibitor, (ii) a CAI, and (iii) at least one cholesterol lowering drug selected from the group consisting of a HMG-CoA reductase inhibitor, a bile acid sequestrant, a fibric acid derivative, niacin, and squalene sythetase inhibitor. When three active ingredients are used, this is referred to as a triple combination. However, it is contemplated that more than three of the active ingredients can be used in the practice of the invention.

[0031] In another aspect, the composition comprises (i) and MTP inhibitor, (ii) a HMG-CoA reductase inhibitor, and (iii) at least one cholesterol lowering drug selected from the group consisting of a bile acid sequestrant, a fibric acid derivative, niacin, and squalene synthetase inhibitor. It is contemplated that more than three of the active ingredients can be used in the practice of the invention.

[0032] It is contemplated that the combination of active

lower dosages of the individual active ingredients thereby reducing the incidence and/or severity of dose-related adverse events associated with the individual active ingredients. It is contemplated that, for example, lowering blood LDL levels below those already achieved in earlier clinical trials by using, for example, an MTP inhibitor in combination with a HMG-CoA reductase inhibitor plus a CAI will provide further improvements in cardiovascular event rate reduction and/or plaque regression

[0033] For example, the compositions can be used to reduce the fasting levels of cholesterol and/or triglycerides in the blood of a mammal to meet a clinical end-point but with fewer or reduced adverse events than (i) when the MTP inhibitor is administered alone in a monotherapy at a dosage sufficient to achieve or substantially achieve (for example, within 10%) the clinical end-point or (ii) when the MTP inhibitor is administered together with another cholesterol lowering agent, where the MTP inhibitor and the other cholesterol lowering agent are administered at dosages sufficient to achieve or substantially achieve the clinical end-point.

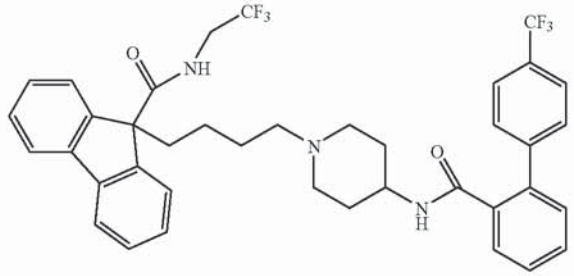
[0034] Furthermore, the compositions can be used to reduce by at least 55%, 60%, or 65%, the blood LDL concentration in a population of patients who, prior to therapy have circulating LDL concentrations of at least 130 mg/dL, so as to meet the goal of having an LDL concentration of 70 mg/dL or less, where (i) less than 2% of the patients in the population have Liver Function Test results three times greater than the upper limit of normal of a standard clinical laboratory range or (ii) the patients have statistically significant lower rates of skeletal muscle side effects (e.g., myalgia and/or myopathy) relative to patients receiving the maximum permitted dose of a HMG-CoA reductase inhibitor.

[0035] Furthermore, it is contemplated that the compositions, when administered to the recipient, will not only permit the recipient to meet a cholesterol goal but will also slow down or stop the build up of plaques, for example, atherosclerotic plaques, on the walls of blood vessels. Under certain circumstances, it is contemplated that the compositions, when administered, will also induce regression of existing plaques.

[0036] Preferred active agents that can be combined to meet the clinical end points described herein are set forth below.

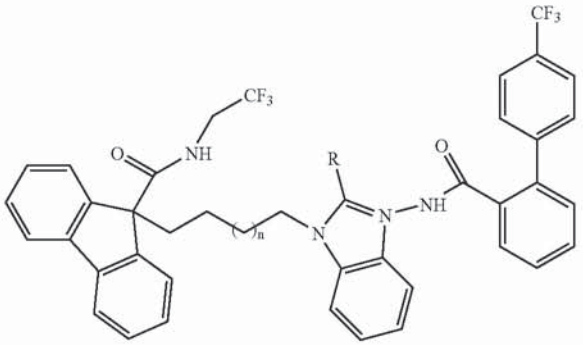
[0037] A. MTP Inhibitors

[0038] In one embodiment, the MTP inhibitor may be BMS 201038 (denoted as M1). As used herein, the phrase "BMS-201038" refers to a compound known as N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'biphenyl]-2-Yl] carbonyl]amino]-1-piperidinyl]butyl]9H-fluorene-9-carboxamide, having the formula:



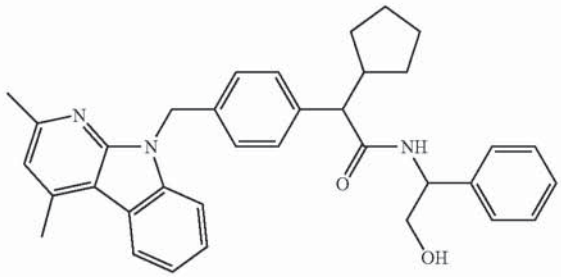
and stereoisomers thereof, and pharmaceutically acceptable salts and esters thereof.

[0039] In another embodiment, the MTP inhibitor may include benzimidazole-based analogues of BMS 201038 (denoted as M2). As used herein, the "M2" refers to a compound having the formula shown below:



where n can be 0 to 10, and stereoisomers thereof, and pharmaceutically acceptable salts and esters thereof.

[0040] In another embodiment, the MTP inhibitor may be implitapide (denoted as M3). As used herein, the phrase "implitapide" refers to a compound (2S)-2-cyclopentyl-2-[4-[(2,4-dimethyl-9H-pyrido[2,3-b]indol-9-yl)methyl]phenyl]-N-[(1S)-2-hydroxy-1-phenylethyl]ethanamide, and having the structure shown below:



and stereoisomers thereof, and pharmaceutically acceptable salts and esters thereof.

[0041] In another embodiment, the MTP inhibitor may be JTT-130m (denoted as M4) including pharmaceutically acceptable salts and esters thereof, described in Aggarwal, et al., BMC CARDIOVASC. DISORD. 27;5(1):30 (2005). In another embodiment, the MTP inhibitor may be CP-346086 (denoted M5) including pharmaceutically salts and esters thereof, described in Chandler, et al., J. LIPID. RES. 44(10):1887-901 (2003).

[0042] Other MTP inhibitors include those developed by Surface Logix, Inc. e.g., SLx-4090 (denoted as M6).

[0043] B. Other Cholesterol Lowering Agents

[0044] Cholesterol lowering agents that may be used in the compositions and methods described herein include:

[0045] 1. Cholesterol Absorption Inhibitors (CAI)

[0046] In one embodiment, the CAI may be ezetimibe (also known as Zetia) (denoted as C1), As used herein, the phrase

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