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(54) Title: PHARMACEUTICAL COMBINATIONS FOR LIPID MANAGEMENT AND IN THE TREATMENT OF ATHEROSCLEROSIS AND HEPATIC STEATOSIS

(57) Abstract: A pharmaceutical combination comprising an effective amount of at least one cholesterol absorption inhibitor and at least one microsomal triglyceride transfer protein inhibitor (MTP)

WO 2008/030382 A1

PHARMACEUTICAL COMBINATIONS FOR LIPID MANAGEMENT AND IN THE TREATMENT OF ATHEROSCLEROSIS AND HEPATIC STEATOSIS

RELATED APPLICATIONS

This application claims priority to provisional application USSN 60/842,211, filed on September 5, 2006, herein incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to pharmaceutical combinations which are used in lipid management of a mammal, such as a human, and in the treatment of atherosclerosis and hepatic steatosis by administering an effective amount of the pharmaceutical combination. The pharmaceutical combinations comprise at least one cholesterol absorption inhibitor (CAI) and a microsomal triglyceride transfer protein (MTP) inhibitor.

BACKGROUND OF THE INVENTION

Vascular disease is a term which broadly encompasses all disorders of blood vessels including small and large arteries and veins and blood flow. The most prevalent form of vascular disease is arteriosclerosis, a condition associated with the thickening and hardening of the arterial wall. Arteriosclerosis of the large vessels is referred to as atherosclerosis. Atherosclerosis is the predominant underlying factor in vascular disorders such as coronary artery disease, aortic aneurysm, arterial disease of the lower extremities and cerebrovascular disease.

One major risk factor for arteriosclerosis is high serum cholesterol. A total cholesterol level in excess of 225-250 mg/dl is associated with significant elevation of risk of vascular disease, particularly coronary heart disease.

Cholesteryl esters are a major component of atherosclerotic lesions and the major storage form of cholesterol in arterial wall cells. Formation of cholesteryl esters is also a step in the intestinal absorption of dietary cholesterol. Thus, inhibition of cholesteryl ester formation and reduction of serum cholesterol can inhibit the progression of atherosclerotic lesion formation, decrease the accumulation of cholesteryl esters in the arterial wall, and block the intestinal absorption of dietary cholesterol.

The regulation of whole-body cholesterol homeostasis in mammals and animals involves the regulation of dietary cholesterol and modulation of cholesterol biosynthesis, bile acid biosynthesis and the catabolism of the cholesterol-containing plasma lipoproteins. The liver is the major organ responsible for cholesterol biosynthesis and catabolism and, for this reason, it is a prime determinant of plasma cholesterol levels. The liver is the site of synthesis and secretion of very low density lipoproteins (VLDL) which are subsequently metabolized to low density lipoproteins (LDL) in the circulation. LDL are the predominant cholesterol-carrying lipoproteins in the plasma and an increase in their concentration is correlated with increased atherosclerosis. When intestinal cholesterol absorption is reduced, by whatever means, less cholesterol is delivered to the liver. The consequence of this action is decreased hepatic lipoprotein (VLDL) production and an increase in the hepatic clearance of plasma cholesterol, mostly as LDL. Thus, the net effect of inhibiting intestinal cholesterol absorption is a decrease in plasma cholesterol levels.

U.S. Patents Nos. 5,846,966 and 5,661,145, respectively, disclose treatments for inhibiting atherosclerosis and reducing plasma cholesterol levels using such hydroxy-substituted azetidinone compounds or substituted β-lactam compounds in combination with HMG-CoA reductase inhibitor compounds, which act by blocking hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase (the rate-limiting enzyme in hepatic cholesterol synthesis). HMG-CoA reductase inhibitors, e.g., statins such as lovastatin, simvastatin, and pravastatin, slow the progression of atherosclerotic lesions in the coronary and carotid arteries. Simvastatin and pravastatin have also been shown to reduce the risk of coronary heart disease events in patients with hypercholesterolemia and/or atherosclerotic coronary heart disease (CHD).

Simvastatin is marketed worldwide, and sold in the U.S. under the tradename ZOCOR®. Methods for making it are described in U.S Patent Nos. 4,444,784; 4,916,239; 4,820,850; among other patent and literature publications.

U.S. Patent No. 5,698,527 discloses ergostanone derivatives substituted with disaccharides as cholesterol absorption inhibitors, employed alone or in combination with certain other cholesterol lowering agents, which are useful in the treatment of hypercholesterolemia and related disorders.

Other vascular conditions frequently coexist with cholesterol levels associated with atherosclerosis. These may include hypertension, angina and/or arrhythmia.

The relevance of, for example, elevated blood pressure as a risk factor for atherosclerosis, cardiovascular and cerebrovascular disease in both men and women has been clarified in a large number of epidemiological studies.

Clinical trials of blood pressure lowering using cardiovascular agents including, for example, calcium channel blockers, have shown beneficial effects in the treatment of early atherosclerotic lesions (see, e.g., Lichtien, P.R. et al. :Lancet, 335: 1109-1113 (1990) and Waters, D. et al. Circulation 82: 1940-1953 (1990)). Scott (PCT patent Application No. WO 99/11260) describes combinations of an HMG CoA reductase inhibitor with an antihypertensive agent for the treatment of atherosclerosis and other symptoms of vascular disease risk. Additionally, Egon et al. (PCT Patent Application No. WO 96/40255) describe a combination therapy of antihypertensive agents including eplerenone and angiotensin II antagonist for treating cardiovascular disease.

In vitro MTP catalyzes the transport of lipid molecules between phospholipid membranes. *See*, U.S. 6,472,414 B1. *In vivo* it has been reported that MTP mediates trigyceride absorption and chylomicron secretion from the intestine and VLDL secretion from the liver, by linking lipid molecules with apolipoprotein B (ApoB). (See, abstract of S. Williams & J.D. Best, Expert Opinion on Therapeutic Patents (April 2003, vol.13, no. 4, pp. 470-488), www.expertopin. com/doi/abs /10.1517 /13543776.13.4.479 ?cookieSet+1&journalCode). It follows that inhibition of MTP could reduce the level of all ApoB-contining proteins, including LDL. Drugs that inhibit MTP, therefore, potentially could be effective in reducing atherosclerotic vascular disease by lowering all levels of atherogenic lipoproteins. One commentator has suggested that while partial inhibition of MTP by an inhibitor could be useful when combined with other drugs that alter lipid metabolism, marked inhibition of MTO could cause significant adverse effects (Williams & Best).

Substances that inhibit MTP are well known in the art. See US 2006/0166999 A1 and US 6,472,414 B2, both herein incorportated by reference, which cites to EP 705 831, EP 779 279, EP 779 276, EP 802 198 and EP 799 828, also incorporated by reference. Zaiss et al., *Circulation*, 100 (18 Suppl. I): 255 Abst. 13423 (1999) reports that implitiapide, a MTP inhibitor, prevents the formation of atherosclerotic plaques in mice.

WO 2005/087234 A1, incorporated by reference, discloses method and compositions for treating hyprlipidemia and/or hypercholesterolemia that comprise

administering to the subject and effective amount of an MTP inhibitor, wherein said administration comprises at least three step-wise, increasing dosages of the MTP inhibitor; the MTP inhibitor may be combined with a further lipid modifying compound, such as a HMG Co-A reductase inhibitor or ezetimibe.

WO 00/38725 A1, incorporated by reference, discloses cardiovascular therapeutic combinations including an ileal bile acid transport inhibitor or cholesteryl ester transport protein inhibitor in combination with a fibric acid derivative, nicotinic acid derivative, microsomal triglyceride transfer protein inhibitor, cholesterol absorption antagonist, phytosterol, stanol, antihypertensive agent or bile acid sequestrant.

Despite recent improvements in the management of lipid levels in mammals, such as humans, as well as for the treatment for atherosclerosis, hyperlipidemia, lyperlipenia, hypertriglyceridemia, other vascular diseases and hepatic steatosis, there remains a need in the art for improved compositions and treatments these disease states.

SUMMARY OF THE INVENTION

The present invention provides for pharmaceutical combinations comprising at least one cholesterol absorption inhibitor, e.g., a sterol absorption inhibitor or a 5-α-stanol absorption inhibitor, and at least one microsomal triglyceride transfer protein inhibitor.

The present invention also provides for a method for lipid management in a mammal in need thereof which comprises administering an effective amount of a pharmaceutical combination comprising at least one cholesterol absorption inhibitor, e.g., a sterol absorption inhibitor or a 5-α-stanol absorption inhibitor, and at least one microsomal triglyceride transfer protein inhibitor.

An alternative embodiment of the present invention also provides for a method for the treatment, prevention or ameliorating the symptoms atherosclerosis in a mammal in need thereof by administering an effective amount of a composition comprising at least one cholesterol absorption inhibitor, e.g., a sterol absorption inhibitor, a 5-α-stanol absorption inhibitor, and at least one microsomal triglyceride transfer protein inhibitor.

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