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(54) Title: MTP INHIBITORS AND FAT SOLUBLE VITAMIN THERAPEUTIC COMBINATIONS TO LOWER SERUM LIPID LEVELS

(57) Abstract

A pharmaceutical combination formed of an MTP inhibitor and a fat soluble vitamin such as Vitamins E, A, K and/or D, and optionally another cholesterol lowering drug, is provided which is employed in a method for lowering serum lipids, cholesterol and/or triglycerides and thereby inhibiting or treating atherosclerosis, pancreatitis, hyperglycemia and/or obesity.

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MTP INHIBITORS AND FAT SOLUBLE VITAMIN THERAPEUTIC COMBINATIONS TO LOWER SERUM LIPID LEVELS.

Field of the Invention

The present invention relates to a combination of an MTP inhibitor and a fat soluble vitamin such as Vitamin E, Vitamin A, Vitamin K and/or Vitamin D, and optionally another cholesterol lowering drug, for example, an HMG CoA reductase inhibitor, such as pravastatin, lovastatin or simvastatin, and to a method for lowering serum lipids, cholesterol and/or triglycerides in mammalian species by administering such combination.

Background of the Invention

The use of microsomal triglyceride transfer protein (MTP) inhibitors for decreasing serum lipids including cholesterol and triglycerides and their use in treating atherosclerosis, obesity and pancreatitis is disclosed in Canadian Patent Application No. 2,091,102 (corresponding to U.S. Application Serial No. 117,362), U.S. Application Serial No. 472,067, filed June 6, 1995 (file DC21e), U.S. Application Serial No. 548,811, filed January 11, 1996 (file DC21h), U.S. Application Serial No. 08/767,923, filed December 17, 1996 (file HX79c*), U.S. provisional application No. 60/017,253, (file HX82*) and U.S. provisional application No. 60/017,254, (file HX84*).

All of the above U.S. applications are incorporated herein by reference.

Description of the Invention

In accordance with the present invention, a novel combination is provided which includes an MTP inhibitor and a fat soluble vitamin such as Vitamin E, Vitamin A, Vitamin K and/or Vitamin D, and optionally another cholesterol lowering agent.

In addition, in accordance with the present invention, a method for preventing, inhibiting or treating atherosclerosis, pancreatitis, hyperglycemia, or obesity is provided, wherein an MTP inhibitor in combination with a fat soluble vitamin such as Vitamin E, Vitamin A, Vitamin K and/or Vitamin D, and optionally another cholesterol lowering drug, is administered in therapeutically effective amounts to lower LDL cholesterol and triglycerides.

Furthermore, in accordance with the present invention, a method is provided for lowering serum lipid levels, cholesterol and/or triglycerides, or inhibiting and/or treating hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia, wherein a combination of an MTP inhibitor and a fat soluble vitamin such as Vitamin E, Vitamin A, Vitamin K and/or Vitamin D, and optionally another cholesterol lowering drug, is administered in therapeutically effective amounts.

MTP inhibitors inhibit the production of triglyceride rich plasma lipoproteins, very low density lipoproteins (VLDL) and chylomicrons. Vitamins E, A, K and D are fat soluble vitamins which are, in part, transported throughout the body on these lipoproteins, or lipoproteins which are metabolic products of these lipoproteins. Because MTP inhibitors block lipoprotein production, they may interfere with the normal absorption and transport of fat soluble vitamins. Abnormal absorption of fat soluble vitamins has been observed in abetalipoproteinemic subjects who lack MTP due to a genetic defect in the gene encoding MTP. Fat soluble vitamin supplements in abetalipoproteinemic subjects ameliorate most if not all the complications associated with fat soluble vitamin deficiencies (Kane, J.P., et al, "Disorders of the Biogenesis and Secretion of Lipoproteins Containing the B Apolipoproteins", Chapter 57, pp. 1853-1885, "The Metabolic and Molecular Bases of Inherited Disease", 7th Ed., Vol. 11 (1995)). Thus, Vitamins E, A, K, and/or D supplements in

subjects treated with an MTP inhibitor will ameliorate adverse effects of MTP inhibitors associated with fat soluble vitamin deficiencies.

Cholesterol lowering drugs or drugs which are inhibitors of cholesterol biosynthesis which may optionally be used in combination with the MTP inhibitor and the fat soluble vitamin include HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, bile acid sequestrants, probucol, niacin, niacin derivatives, neomycin, aspirin, and the like.

It is believed that the combination of MTP inhibitor and other cholesterol lowering drug, which works by a mechanism other than inhibiting MTP, together with a fat soluble vitamin is a surprising and unique concept in treating diseases involved with elevated cholesterol and/or triglycerides and atherosclerosis, hyperglycemia, obesity and/or pancreatitis, in that the combination may provide additional anticholesterolemic effects over that which may be obtained using each of the cholesterol lowering components of the combination alone. It is expected that reduced levels of each of the MTP inhibitor and other cholesterol lowering drug may be employed to achieve desired results, albeit with reduced side effects.

Detailed Description of the Invention

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

The term "MTP" refers to a polypeptide or protein complex that (1) if obtained from an organism (e. g., cows, humans, etc.), can be isolated from the microsomal fraction of homogenized tissue; and (2) stimulates the transport of triglycerides, cholesterol esters, or phospholipids from synthetic phospholipid vesicles, membranes or lipoproteins to synthetic vesicles, membranes, or lipoproteins and which is distinct from the cholesterol ester transfer protein

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