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(12) **United States Patent**
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(54) **METHODS FOR TREATING DISORDERS OR DISEASES ASSOCIATED WITH HYPERLIPIDEMIA AND HYPERCHOLESTEROLEMIA WHILE MINIMIZING SIDE EFFECTS**

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See application file for complete search history.

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(57) **ABSTRACT**

The present invention provides methods and compositions for treating hyperlipidemia and/or hypercholesterolemia comprising administering to the subject an effective amount of an MTP inhibitor to inhibit hyperlipidemia and/or hypercholesterolemia in said subject, wherein said administration comprises an escalating series of doses of the MTP inhibitor. In some embodiments the method comprises administering at least three step-wise, increasing dosages of the MTP inhibitor to the subject. In some embodiments, the method further comprises the administration of one or more other lipid modifying compounds.

**10 Claims, No Drawings**

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# METHODS FOR TREATING DISORDERS OR DISEASES ASSOCIATED WITH HYPERLIPIDEMIA AND HYPERCHOLESTEROLEMIA WHILE MINIMIZING SIDE EFFECTS

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 10/591,923, which is a national phase application under 35 U.S.C. §371 of PCT/US05/007435 filed Mar. 7, 2005 which in turn claims priority benefit of U.S. Ser. No. 60/550,915, filed Mar. 5, 2004, all of which are hereby incorporated by reference in their entireties.

## FIELD OF THE INVENTION

The present invention generally relates to therapy for hypercholesterolemia and hyperlipidemia.

## BACKGROUND OF THE INVENTION

Hypercholesterolemia is a well-known risk factor for ASCVD, the major cause of mortality in the Western world. Numerous epidemiological studies have clearly demonstrated that pharmacological lowering of total cholesterol (TC) and Low-density Lipoprotein (LDL) Cholesterol (LDL-C) is associated with a significant reduction in clinical cardiovascular events. Hypercholesterolemia is often caused by a polygenic disorder in the majority of cases and modifications in lifestyle and conventional drug treatment are usually successful in reducing cholesterol levels. However, in few cases, as in familial hypercholesterolemia (FH), the cause is a monogenic defect and the available treatment in homozygous patients can be much more challenging and far from optimal because LDL-C levels remain extremely elevated despite aggressive use of combination therapy. Therefore, for this group of high-risk patients, effective medical therapy is urgently needed.

Triglycerides are common types of fats (lipids) that are essential for good health when present in normal amounts. They account for about 95 percent of the body's fatty tissue. Abnormally high triglyceride levels may be an indication of such conditions as cirrhosis of the liver, underactive thyroid (hypothyroidism), poorly controlled diabetes, or pancreatitis (inflammation of the pancreas). Researchers have identified triglycerides as an independent risk factor for heart disease.

Higher-than-normal triglyceride levels are often associated with known risk factors for heart disease, such as low levels of HDL ("good") cholesterol, high levels of LDL ("bad") cholesterol and obesity. Triglycerides may also contribute to thickening of artery walls—a physical change believed to be a predictor of atherosclerosis.

Therefore, high triglyceride levels are at least a warning sign that a patient's heart health may be at risk. In response, physicians may be more likely to stress the importance of losing weight, getting enough exercise, quitting smoking, controlling diabetes and other strategies that patients can use to protect their own cardiovascular health.

A large number of genetic and acquired diseases can result in hyperlipidemia. They can be classified into primary and secondary hyperlipidemic states. The most common causes of the secondary hyperlipidemias are diabetes mellitus, alcohol abuse, drugs, hypothyroidism, chronic renal failure, nephrotic syndrome, cholestasis and bulimia. Primary hyperlipidemias have also been classified into common hypercholesterolemia, familial combined hyperlipidemia, familial hypercholesterolemia, remnant hyperlipidemia, chylomicronemia syndrome and familial hypertriglyceridemia.



A number of treatments are currently available for lowering serum cholesterol and triglycerides. However, each has its own drawbacks and limitations in terms of efficacy, side-effects and qualifying patient population.

Bile-acid-binding resins are a class of drugs that interrupt the recycling of bile acids from the intestine to the liver; e.g., cholestyramine (Questran Light®, Bristol-Myers Squibb), and colestipol hydrochloride (Colestid®, The Upjohn Company). When taken orally, these positively-charged resins bind to the negatively charged bile acids in the intestine. Because the resins cannot be absorbed from the intestine, they are excreted carrying the bile acids with them. The use of such resins, however, at best only lowers serum cholesterol levels by about 20%, and is associated with gastrointestinal side-effects, including constipation and certain vitamin deficiencies. Moreover, since the resins bind other drugs, other oral medications must be taken at least one hour before or four to six hours subsequent to ingestion of the resin; thus, complicating heart patient's drug regimens.

The statins are cholesterol-lowering agents that block cholesterol synthesis by inhibiting HMGCoA reductase—the key enzyme involved in the cholesterol biosynthetic pathway. The statins, e.g., lovastatin (Mevacor®, Merck & Co., Inc.), simvastatin (Zocor®, Merck & Co., Inc.), atorvastatin (Lipitor®, Pfizer), rosuva (Crestor®, Astra Zeneca) and pravastatin (Pravachol®, Bristol-Myers Squibb Co.), and combinations thereof are sometimes used in combination with bile-acid-binding resins. Statins significantly reduce serum cholesterol and LDL-serum levels, and slow progression of coronary atherosclerosis. However, serum HDL cholesterol levels are only moderately increased. The mechanism of the LDL lowering effect may involve both reduction of VLDL concentration and induction of cellular expression of LDL-receptor, leading to reduced production and/or increased catabolism of LDLs. Side effects, including liver and kidney dysfunction are associated with the use of these drugs (Physicians Desk Reference, Medical Economics Co., Inc., Montvale, N.J., 2004; hereinafter "PDR"). The FDA has approved atorvastatin to treat rare but urgent cases of familial hypercholesterolemia.

Ezetimibe is a cholesterol absorption inhibitor which reduces the amount of cholesterol absorbed by the body. Ezetimibe is used to reduce the amount of total cholesterol, LDL cholesterol (by about 18%), and apolipoprotein B. Ezetimibe is often used with a low cholesterol diet and, in some cases, other cholesterol lowering medications.

Niacin, or nicotinic acid, is a water soluble vitamin B-complex used as a dietary supplement and antihyperlipidemic agent. Niacin diminishes production of VLDL and is effective at lowering LDL. In some cases, it is used in combination with bile-acid binding resins. NIASPAN® has been approved to prevent recurrent heart attacks in patients with high cholesterol. Niacin can increase HDL when used at adequate doses, however, its usefulness is limited by serious side effects when used at such high doses.

Fibric acid derivatives ("fibrates") are a class of lipid-lowering drugs used to treat various forms of hyperlipidemia (i.e., elevated serum triglycerides) which may also be associated with hypercholesterolemia. Fibrates appear to reduce the VLDL fraction and modestly increase HDL. However, the effects of these drugs on serum cholesterol is variable. Fibrates are mainly used to lower high triglyceride levels. Although fibrates typically do not appear as effective as statins in lowering total cholesterol and LDL cholesterol lev-

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