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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : A01N 43/16, 43/18, 43/40, A61K 31/35, 31/38, 31/445</p>	<p>A1</p>	<p>(11) International Publication Number: WO 98/03069 (43) International Publication Date: 29 January 1998 (29.01.98)</p>
<p>(21) International Application Number: PCT/US97/12229 (22) International Filing Date: 14 July 1997 (14.07.97) (30) Priority Data: 60/022,866 24 July 1996 (24.07.96) US (71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US). (72) Inventors: GREGG, Richard, E.; 7 Linden Lane, Pennington, NJ 08543 (US). POULEUR, Hubert, G.; 43 Woodlane Road, Lawrenceville, NJ 08648 (US). WETTERAU, John, R., II; 190 Rugby Drive, Langhorne, PA 19047 (US). (74) Agents: RODNEY, Burton et al.; Bristol-Myers Squibb Com- pany, P.O. Box 4000, Princeton, NJ 08543-4000 (US).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>	
<p>(54) Title: METHOD FOR LOWERING SERUM LIPID LEVELS EMPLOYING AN MTP INHIBITOR IN COMBINATION WITH ANOTHER CHOLESTEROL LOWERING DRUG</p>		
<p>(57) Abstract</p> <p>A method is provided for lowering serum lipids, cholesterol and/or triglycerides and thereby inhibiting atherosclerosis by administering to a patient an MTP inhibitor, in combination with a cholesterol lowering drug, such as pravastatin.</p>		

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METHOD FOR LOWERING SERUM LIPID LEVELS
EMPLOYING AN MTP INHIBITOR IN COMBINATION WITH
ANOTHER CHOLESTEROL LOWERING DRUG

5 Field of the Invention

The present invention relates to a method
for lowering serum lipids, cholesterol and/or
triglycerides in mammalian species by administering
an MTP inhibitor in combination with another
10 cholesterol lowering drug, for example, an HMG CoA
reductase inhibitor, such as pravastatin,
lovastatin or simvastatin.

Background of the Invention

15 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
20 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 (file
DC21h), U.S. provisional application No.
25 60/017,224, (file HX79a*), 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
30 incorporated herein by reference.

Description of the Invention

In accordance with the present invention, a
method for preventing, inhibiting or treating
35 atherosclerosis, pancreatitis or obesity is
provided, wherein an MTP inhibitor in combination

with 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, hyperlipid-emia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia, wherein a combination of an MTP inhibitor and another cholesterol lowering drug is administered in therapeutically effective amounts.

In addition, in accordance with the present invention, a novel combination of cholesterol lowering agents is provided which includes an MTP inhibitor and another cholesterol lowering drug.

Cholesterol lowering drugs or drugs which are inhibitors of cholesterol biosynthesis which may be used in the method of the invention in combination with the MTP inhibitor 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, is a surprising and unique concept in treating diseases involved with elevated cholesterol and/or triglycerides and atherosclerosis, obesity and/or pancreatitis, in that the combination may provide additional anticholesterolemic effects over that which may be obtained using each of the 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

5 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
10 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,
15 membranes or lipoproteins to synthetic vesicles, membranes, or lipoproteins and which is distinct from the cholesterol ester transfer protein [Drayna et al., Nature 327, 632-634 (1987)] which may have similar catalytic properties.

20 The phrase "stabilizing" atherosclerosis as used in the present application refers to slowing down the development of and/or inhibiting the formation of new atherosclerotic lesions.

The phrase "causing the regression of"
25 atherosclerosis as used in the present application refers to reducing and/or eliminating atherosclerotic lesions.

The combination of the MTP inhibitor and other cholesterol lowering drug will be employed in
30 a weight ratio to each other of within the range of from about 1000:1 to about 0.001:1 and preferably from about 0.05:1 to about 100:1.

MTP inhibitors to be employed in the methods of the invention include MTP inhibitors
35 disclosed in Canadian Patent Application No. 2,091,102 (corresponding to U.S. Application Serial

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