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

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(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).

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

RELATED APPLICATIONS

[0001] This application claims priority to provisional application U.S. Ser. No. 60/842,211, filed on Sep. 5, 2006, herein incorporated by reference.

FIELD OF THE INVENTION

[0002] 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

[0003] 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.

[0004] 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.

[0005] 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.

[0006] 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 cho-

[0007] U.S. Pat. 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).

[0008] Simvastatin is marketed worldwide, and sold in the U.S. under the tradename ZOCOR®. Methods for making it are described in U.S. Pat. Nos. 4,444,784; 4,916,239; 4,820,850; among other patent and literature publications.

[0009] U.S. Pat. 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.

[0010] 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.

[0011] 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.

[0012] In vitro MTP catalyzes the transport of lipid molecules between phospholipid membranes. See, U.S. Pat. No. 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-containing 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).

[0013] Substances that inhibit MTP are well known in the

B2, both herein incorporated 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.

[0014] WO 2005/087234 A1, incorporated by reference, discloses method and compositions for treating hyperlipidemia and/or hypercholesterolemia that comprise administering to the subject and effective amount of an MTP inhibitor, wherein said administration comprises at least three stepwise, 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.

[0015] 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.

[0016] 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

[0017] 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.

[0018] 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.

[0019] 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.

[0020] Another embodiment of this invention provides for the mitigation, prevention or amelioration the symptoms or development of hepatic steatosis in a mammal in need thereof by administering 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.

[0021] Another embodiment of the present invention also provides for a method for the treatment, prevention or amelioration of the symptoms atherosclerosis 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, at least one microsomal triglyceride transfer protein inhibitor and at least one cholesterol lowering agent, e.g., a HMG-CoA reductase inhibitor.

[0022] A further embodiment of the present invention 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, or a 5-α-stanol absorption inhibitor, at least one microsomal triglyceride transfer protein inhibitor and at least one cholesterol lowering agent, e.g., a HMG-CoA reductase inhibitor.

[0023] Another embodiment of this invention provides for the mitigation, prevention or amelioration the symptoms or development of hepatic steatosis in a mammal in need thereof by administering at least one cholesterol absorption inhibitor, e.g., a sterol absorption inhibitor or a 5-α-stanol absorption inhibitor, at least one microsomal triglyceride transfer protein inhibitor, and at least one cholesterol lowering agent, e.g., a HMG-CoA reductase inhibitor.

[0024] The present invention also relates to a kit for lipid management in a mammal or for the treatment, prevention or amelioration of the symptoms of atherosclerosis or hepatic steatosis which comprises at least one cholesterol absorption inhibitor and at least one microsomal triglyceride transfer protein inhibitor in separate form.

DETAILED DESCRIPTION

[0025] The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims: Chemical names, common names and chemical structures may be used interchangeably to describe that same structure. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated Hence, the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portion of "hydroxyalkyl", "haloalkyl", "alkoxy" etc.

[0026] As used above, and throughout the specification, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

[0027] "Patient" includes both human and animals.

[0028] "Mammal" means humans and other mammalian animals.

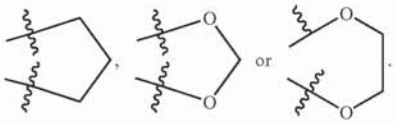
[0029] "Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkyl groups

n-pentyl, heptyl, nonyl and decyl. R^{32}-substituted alkyl groups include fluoromethyl, trifluoromethyl and cyclopropylmethyl.

[0030] "Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

[0031] "Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched, Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl, 3-methylbutynyl, n-pentynyl, and decynyl.

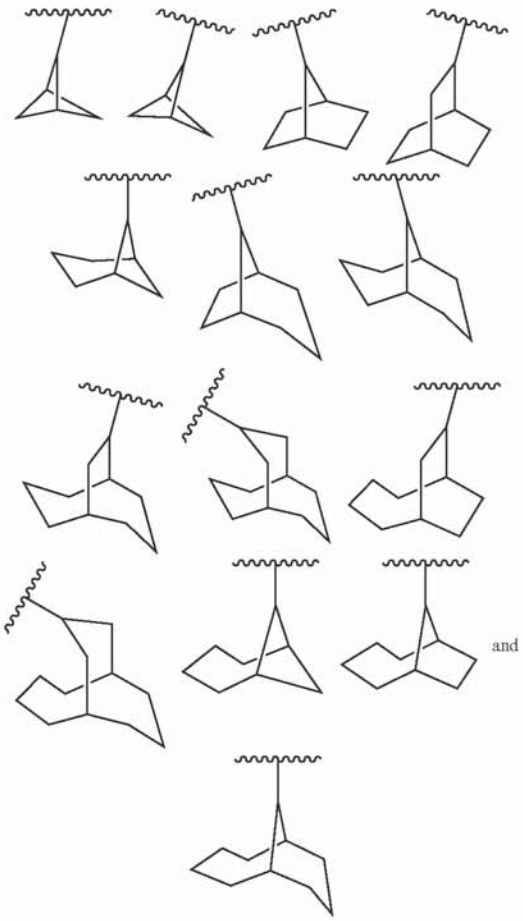
[0032] "Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more substituents, which may be the same or different, and are as defined herein or two substituents on adjacent carbons can be linked together to form



Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

[0033] "Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one to four of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more substituents, which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like.

[0034] "Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more substituents which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalin, norbornyl, adamantyl and the like. Further non-limiting examples of cycloalkyl include the following:



[0035] "Cycloalkylether" means a non-aromatic ring of 3 to 7 members comprising an oxygen atom and 2 to 7 carbon atoms. Ring carbon atoms can be substituted, provided that substituents adjacent to the ring oxygen do not include halo or

[0036] "Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. The cycloalkenyl ring can be optionally substituted with one or more substituents which may be the same or different, and are as defined above. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like, Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

[0037] "Heterocyclenyl" (or "heterocycloalkeneyl") means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be optionally substituted by one or more substituents. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic azaheterocyclenyl groups include 1,2,3,4-tetrahydropyridyl, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridyl, 1,4,5,6-tetrahydropyrimidyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, and the like. Non-limiting examples of suitable oxaheterocyclenyl groups include 3,4-dihydro-2H-pyran, dihydrofuranyl, fluorodihydrofuranyl, and the like. Non-limiting example of a suitable multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl. Non-limiting examples of suitable monocyclic thiaheterocyclenyl rings include dihydrothiophenyl, dihydrothiopyranyl, and the like.

[0038] "Halo" means fluoro, chloro, bromo, or iodo groups. Preferred are fluoro, chloro or bromo, and more preferred are fluoro and chloro.

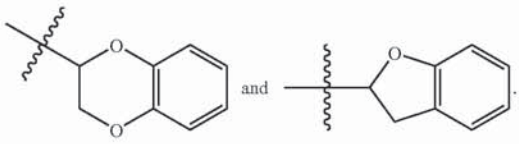
[0039] "Haloalkyl" means an alkyl as defined above wherein one or more hydrogen atoms on the alkyl is replaced by a halo group defined above.

[0040] "Heterocyclyl" (or heterocycloalkyl) means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which 1-3, preferably 1 or 2 of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclyl can be optionally substituted by one or more which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

[0041] "Arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

[0042] "Arylcycloalkyl" means a group derived from a fused aryl and cycloalkyl as defined herein. Preferred arylcycloalkyls are those wherein aryl is phenyl and cycloalkyl consists of about 5 to about 6 ring atoms. The arylcycloalkyl can be optionally substituted by one or more substituents. Non-limiting examples of suitable arylcycloalkyls include indanyl and 1,2,3,4-tetrahydronaphthyl and the like. The bond to the parent moiety is through a non-aromatic carbon atom.

[0043] "Arylheterocycloalkyl" means a group derived from a fused aryl and heterocycloalkyl as defined herein. Preferred arylcycloalkyls are those wherein aryl is phenyl and heterocycloalkyl consists of about 5 to about 6 ring atoms. The arylheterocycloalkyl can be optionally substituted by one or more substituents. Non-limiting examples of suitable arylheterocycloalkyls include



[0044] The bond to the parent moiety is through a non-aromatic carbon atom.

[0045] "Acyl" means an organic group in which the —OH of the carboxyl group is replaced by some other substituent. Suitable non-limiting examples include H—C(O)—, alkyl-C(O)—, alkenyl-C(O)—, alkynyl-C(O)—, aryl-C(O)— or cycloalkyl-C(O)— group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and cyclohexanoyl.

[0046] "Alkoxy" means an alkyl-O— group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and heptoxy. The bond to the parent moiety is through the ether oxygen.

[0047] "Alkyoxyalkyl" means a group derived from an alkoxy and alkyl as defined herein. The bond to the parent moiety is through the alkyl.

[0048] "Arylalkenyl" means a group derived from an aryl and alkenyl as defined herein. Preferred arylalkenyls are those wherein aryl is phenyl and the alkenyl consists of about 3 to about 6 atoms. The arylalkenyl can be optionally substituted

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