INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5:
A61K 45/06, 35/78, 31/785
A61K 31/365, 31/66, 31/275
// (A61K 35/78, 31/66, 31/275)
(A61K 31/785, 31/66, 31/275)
(A61K 31/66, 31/22, 31/215)
A61K 31/19, 31/365 (A61K 31/365)
A61K 31/275) (A61K 31/275)
A61K 31/22, 31/215, 31/19)

(11) International Publication Number: WO 93/13801

A1

(43) International Publication Date: 22 July 1993 (22.07.93)

(21) International Application Number: PCT/US93/00332

(22) International Filing Date: 14 January 1993 (14.01.93)

(30) Priority data:
823,101 17 January 1992 (17.01.92) US
882,401 13 May, 1992 (13.05.92) US

(71) Applicant: THE PROCTOR & GAMBLE COMPANY

(72) Inventor: BROADDUS, Charles, David ; 2186 Quail Hollow, Cincinnati, OH 45240 (US).

(74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45202 (US).


Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: TREATMENT FOR ATHEROSCLEROSIS

(57) Abstract

Combination therapy is employed to decalcify and remove fatty plaque deposits in blood vessels as a treatment for atherosclerosis. Thus, cholesterol-reducing agents such as lovastatin, psyllium, cholestyramine and gemfibrozil are used with agents such as the diphosphonates and polycarboxylates in therapeutic regimens.
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TREATMENT FOR ATHEROSCLEROSIS

TECHNICAL FIELD

The present invention relates to methods and compositions for alleviating atherosclerosis by the administration of agents for decalcifying and agents for removing vascular plaque.

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of co-pending application Serial No. 07/823,101 filed January 17, 1992.

BACKGROUND OF THE INVENTION

The presence of fatty deposits in the vascular system of humans and some lower animals as a result of genetic, dietary or other factors is well documented and comprises the disease state known as atherosclerosis. The development and progressive growth of such so-called fatty atherosclerotic "plaques" to a state of partial or complete vascular blockage can result in progressive debilitation in the patient, followed by coronary occlusion and death. Fortunately, various surgical techniques, including the now well-known "bypass surgery", have been developed to assist patients whose vascular systems have been rendered dysfunctional by the formation of thick, obstructive vascular plaques. However, surgical intervention, though becoming commonplace, is by no means simple, is always expensive, and carries with it substantial risk.

In recent years it has been discovered that proper attention to diet and exercise can reduce blood triglyceride and cholesterol levels in many patients. Moreover, the appropriate use of therapeutic agents of various types which decrease blood cholesterol, total blood triglycerides and/or low density lipoproteins ("LDL's"), has proven to be of substantial benefit to many hypercholesterolemic patients. Importantly, it has recently been discovered that various combinations of diet, exercise, changes in life style and therapeutic agents not only can lower blood cholesterol, but also can actually reverse the build-up of vascular plaque. This discovery means that, under appropriate circumstances, the atherosclerotic patient may be able not only to impede the further development of the atherosclerotic process, but also to reverse the damage that has already been done.

Unfortunately, the reduction or removal of established vascular plaques may not always be possible in some proportion of
atherosclerotic patients. It is known that some vascular plaques begin to calcify, and it now seems reasonable to speculate that such calcified plaques would be refractory to ordinary therapeutic regimens, short of surgery.

The present invention employs agents which reduce the plaque-producing materials such as cholesterol, serum triglycerides, low density lipoproteins, and the like, in conjunction with agents which serve to decalcify vascular plaque. The conjoint use of these two types of agents provides an improved therapeutic regimen for the treatment of atherosclerosis.

BACKGROUND ART

The use of various therapeutic agents in the management of hypercholesterolemia is well-known in the pharmaceutical literature and in medical practice.

The aryloxyisobutyric acids, especially clofibrate, are known as antihyperlipoproteinemics. See THE MERCK INDEX, 11th Ed. at 2374.

The aryloxypentanoic acids, especially gemfibrozil, are known as antihyperlipoproteinemics. See ibid. at 4280.

The substituted naphthalenyl esters of 2-alkylbutanoic acid, especially lovastatin, are known as antihypercholesterolems. See ibid. at 5460. See also the New York Times article at page A-1 "Study Says Drug Reduces Fat Deposits in Arteries," by L. K. Altman.

Psyllium, cholestryamine, polyl polyesters, and combinations thereof, are known to lower cholesterol. See U.S. Patent 4,849,222, July 18, 1989, and European Patent 323,666, both to C. D. Broaddus.


Psyllium derivatives (also referred to as "gums" or "hydrophilic muciloids") of the type employed herein are known commercially as METAMUCIL brand laxative and are described in Goodman and Gilman, The Pharmacologic Basis of Therapeutics 5th Ed. 979 (1975). See also U.S. Patents 3,455,714 and 4,321,263.
The use of cholestyramine resin as adjunctive therapy to diet in the management of patients with elevated cholesterol levels is noted in Remington’s Pharmaceutical Sciences, 15th Ed. Mack Publishing Co. (1975) pp 733-734.

There are a considerable number of United States patents relating to the use of nonabsorbable, nondigestible polyol polyesters of the type optionally employed herein as cholesterol lowering agents. See, especially, U.S. Patents 3,600,186; 4,005,195; 4,005,196 (includes fat-soluble vitamins); 4,034,083 (with fat-soluble vitamins); in various food compositions, e.g., U.S. Patents 4,368,213; 4,461,782; 3,579,548; and in pharmaceutical products, e.g., U.S. Patents 3,954,976; 4,241,054; 4,264,583; and 4,382,924. Manufacturing processes for the polyol polyesters are described in U.S. Patents 3,963,699; 4,517,360; and 4,518,772.

A wide variety of phosphonate compounds and their use to affect the anomalous mobilization and deposition of calcium minerals are known from many published patents. See, for example, U.S. Patents 3,488,419; 3,678,154; 3,678,164 (nitrilotriphosphonates); 3,584,124; 3,662,066; 3,641,246; 3,584,125; 3,719,756; 4,687,768; and European 186,405 published 2 July 1986, which relates to effective pyridyl diphosphonates for use herein. See also U.S. Patents 4,407,761, PROCESS FOR THE PRODUCTION OF OMEGA-AMINO-1-HYDROXYALKYLIDENE-1,1-BISPHOSPHONIC ACID; 4,922,007, PROCESS FOR PREPARING 4-AMINO-1-HYDROXYBUTYLIDENE-1,1-BISPHOSPHONIC ACID OR SALTS THEREOF; 5,019,651, PROCESS FOR PREPARING 4-AMINO-1-HYDROXYBUTYLIDENE-1,1-BISPHOSPHONIC ACID (ABP) OR SALTS THEREOF; and 5,039,819, DIPHOSPHONATE INTERMEDIATE FOR PREPARING AN ANTIHYPERCALCEMIC AGENT; and European Patents 416,689, ACYLOXYMETHYL ESTERS OF BISPHOSPHONIC ACIDS AS BONE RESORPTION INHIBITORS; and 449,405, USE OF BIPHOSPHONIC ACIDS FOR THE TREATMENT OF CALCIUM METABOLISM DISORDERS for other phosphonates which can be used herein.

The effects of various calcium-affecting materials on atherosclerosis have been reported. See: "Comparative Effects of Cetaben (PHB) and Dichloromethylene Diphosphonate (Cl₂MDP) on the Development of Atherosclerosis in the Cynomolgus Monkey," Hollander, et al., Atherosclerosis, 31 (1978) 307-325 Elsevier; "The Effect of Disodium Ethane-1,1-Diphosphonate (EHDp) on a

Various phenol substituted geminal diphosphonates and their use as pharmaceuticals for the treatment of hyperlipidemia are disclosed in EP 0339 237, Nguyen, et al., published November 2, 1989. See also: Nguyen, Niesor and Bentzen "Gem-Diphosphonate and Gem-Phosphonate-Phosphate Compounds with Specific High Density Lipoprotein Inducing Activity", *J. Med. Chem.* 1987, 30, 1426-1433. Various diphosphonate and phosphonophosphate compounds which, themselves, are said to be useful in pharmaceutical compositions to alter lipoprotein profiles in favor of high density lipoproteins are disclosed in U.S. 4,309,364, Bentzen, et al., issued January 5, 1982. EPO 324 421, Biller, published July 19, 1989, relates to certain phosphiny1 phosphonates for use as inhibitors of cholesterol biosynthesis, and thus as hypocholesterolemic agents.

The sequestration of calcium by means of chelators such as nitrilotriacetate, ethylenediaminetetraacetate, and the like, is well-known in the chemical literature.

**SUMMARY OF THE INVENTION**

The present invention encompasses, in an improved method for reducing atherosclerotic plaque build-up in the blood vessels of a
human or animal patient in need of such treatment, comprising administering to said patient one or more primary agents which safely and effectively reduce a plaque-producing member selected from the group consisting of cholesterol, LDL triglycerides, total plasma triglycerides, or mixtures thereof, in said patient, the improvement which comprises additionally administering to said patient an amount of an auxiliary agent which wholly or partially decalcifies said plaque.

In said method, said primary agent can be, for example, but not by way of limitation, a member selected from the group consisting of the aryloxyisobutyric acids, the aryloxypentanoic acids, the substituted naphthalenyl esters of 2-alkylbutanoic acid, and mixtures thereof. Such agents apparently act systemically.

In another mode, said method can employ a primary agent which is a member selected from the group consisting of:

(a) polycationic resins;
(b) psyllium;
(c) nonabsorbable, nondigestible polyol polyesters;
(d) mixtures of (a) and (b);
(e) mixtures of (a) and (c);
(f) mixtures of (b) and (c); and
(g) mixtures of (a), (b), and (c).

Such agents are believed to act, primarily, in a nonsystemic manner, i.e., by removing cholesterol, fats, etc., directly from the gut, or by removal of bile acids.

In the method herein, the auxiliary agent can be, for example, a member selected from the group consisting of the nitrilotriacetates, the geminal diphosphonates, the vicinal di- or poly-phosphonates, and mixtures thereof. A preferred method employs one or more geminal diphosphonates containing at least one hydroxy-substituted diphosphonate moiety.

The invention also encompasses a composition of matter for reducing atherosclerotic plaque, comprising a mixture of a safe and effective amount of:

(a) one or more primary agents which safely and effectively reduce a plaque-producing member selected from the group
consisting of cholesterol, LDL triglycerides, total plasma triglycerides, or mixtures thereof; and

(b) an auxiliary agent which wholly or partially decalcifies said plaque.

Such compositions include, but are not limited to, those wherein said primary agent is a member selected from the group consisting of the aryloxyisobutyric acids, the aroyloxypentanoic acids, the substituted naphthalenyl esters of 2-alkylbutanoic acid, and mixtures thereof.

Such compositions also include those wherein said primary agent is a member selected from the group consisting of:

(a) polycationic resins;
(b) psyllium;
(c) nonabsorbable, nondigestible polyol polyesters;
(d) mixtures of (a) and (b);
(e) mixtures of (a) and (c);
(f) mixtures of (b) and (c); and
(g) mixtures of (a), (b), and (c).

As examples, but not by way of limitation, such compositions include those wherein said auxiliary agent is a member selected from the group consisting of the nitrilotriacetates, the geminal diphosphonates, the vicinal di- or poly-phosphonates, and mixtures thereof. Preferably, the geminal diphosphonate contains at least one hydroxy-substituted diphosphonate moiety.

The invention also encompasses pharmaceutical compositions in kit form for reducing atherosclerotic plaque comprising individual unit doses of:

(a) one or more primary agents which safely and effectively reduce a plaque-producing member selected from the group consisting of cholesterol, LDL triglycerides, total plasma triglycerides, or mixtures thereof; and

(b) an auxiliary agent which wholly or partially decalcifies said plaque.

Such kits include, but are not limited to, those wherein said primary agent is a member selected from the group consisting of the aryloxyisobutyric acids, the aroyloxypentanoic acids, the substituted naphthalenyl esters of 2-alkylbutanoic acid, and mixtures thereof.
Such kits also include those wherein said primary agent is a member selected from the group consisting of:

(a) polycationic resins;
(b) psyllium;
(c) nonabsorbable, nondigestible polyol polyesters;
(d) mixtures of (a) and (b);
(e) mixtures of (a) and (c);
(f) mixtures of (b) and (c); and
(g) mixtures of (a), (b), and (c).

As examples, but not by way of limitation, such kits include those wherein said auxiliary agent is a member selected from the group consisting of the nitrilotriacetates, the geminal diphosphonates, the vicinal di- or poly-phosphonates, and mixtures thereof. Preferably, the geminal diphosphonate contains at least one hydroxy-substituted diphosphonate moiety.

All ratios, ranges and proportions herein are by weight, unless otherwise specified. All cited patent documents are incorporated herein by reference.

**DETAILED DESCRIPTION OF THE INVENTION**

It will be appreciated by the skilled reader that the "primary" agents used herein to reduce cholesterol, total plasma triglycerides and/or LDL triglycerides can be any such agent which is safe and effective for its intended purpose. Many such primary agents are known in the literature, and the listing which follows is by way of providing illustrations of some preferred and effective agents, but is not intended to be limiting of the scope of such agents which can be used herein. Likewise, the "auxiliary" agent used herein to decalcify vascular plaque can be any agent which is safe and effective for its intended decalcifying purpose. Many auxiliary agents which sequester or otherwise affect calcification are known in the literature, and the listing which follows is by way of providing illustrations of some preferred and effective auxiliary agents, but is not intended to be limiting of the scope of such agents which can be used herein.

I. AGENTS FOR REDUCING CHOLESTEROL, LDL TRIGLYCERIDES, TOTAL BLOOD TRIGLYCERIDES, AND THE LIKE.
Aryloxyisobutyric acids - See Thorp and Waring, *Nature, Lond.* (1962) 194,948-959 and *J. Atheroscler. Res.* 1963, 3, 351, for agents of this type. A preferred aryloxyisobutyric acid comprises Clofibrate, which is ethyl p-chlorophenoxyisobutyrate, available under various trademarks such as AMOTIL, CLOFINIT, REGELAN, and others.

Aryloxypentanoic acids - See U.S. Patents 3,674,836; 4,126,637 and German 1,925,423. A preferred aryloxypentanoic acid comprises Gemfibrozil, which is 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid, available under various trademarks such as LOPID, LIPOZID, GEVILOX, and others.

Substituted naphthalenyl esters of 2-alkylbutanoic acids - See U.S. Patent 4,231,938. A preferred material comprises Lovastatin, which is 2β, 6α-dimethyl-8α-(2-methyl-1-oxobutoxy)-mevinic acid lactone, available under various trademarks such as MEVACOR, MEVINACOR, and others.

Psyllium - Psyllium gum comes from psyllium seed, of plants of the *Plantago* genus. Various species such as *Plantago lanceolata*, *P. rugelii*, and *P. major*, are known. Commercial psyllium includes the French (black; *Plantago indica*), Spanish (*P. psyllium*) and Indian (blond; *P. ovata*). The gum content of the psyllium varies: French psyllium, 11.8%; Indian psyllium, 30.9%; and German psyllium, 11.5%. Indian (blond) psyllium is preferred for use herein. The psyllium gum (or "hydrophilic muciloid") is located in the seed coat, from which it is readily extractable by water. Thus, intact or macerated seeds can be used in the practice of this invention; however, it is more typical to remove the seed coats from the rest of the seed by, for example, slight mechanical pressure, and then to use only the coats as a source of the gum. In the practice of the present invention it is convenient and typical to use macerated seed coats in the final formulation as the source of the psyllium seed gum, but, in an alternative procedure, the seed coats are extracted with water to remove the desired gum for use in the compositions and methods herein.

Polycationic resins - This class of primary agents useful herein includes resin materials such as cholestryamine and colestipol. Cholestryamine resin is a strongly basic anion...
exchange resin consisting of styrenedivinylbenzene copolymer with quaternary ammonium functional groups, prepared by co-polymerizing polystyrene trimethylbenzylammonium chloride through cross-linkage with divinylbenzene. Cholestyramine resin USP is commercially available under the trademarks CUEMID (MSD) and QUESTRAN (Mead-Johnson). Colestipol (colestipol hydrochloride) is a copolymer of diethylpentamine and epichlorohydrin. It is available under trademarks such as COLESTID and LESTID. See U.S. Patent 3,692,895.

Polyl polyesters - The nonabsorbable, nondigestible polyl polyesters (or, simply, polyesters) employed in this invention comprise certain polyols, especially sugars or sugar alcohols, esterified with at least four fatty acid groups. Accordingly, the polyl starting material must have at least four esterifiable hydroxyl groups. Examples of preferred polyols are sugars, including monosaccharides and disaccharides, and sugar alcohols. Examples of monosaccharides containing four hydroxyl groups are xylose and arabinose and the sugar alcohol derived from xylose, which has five hydroxyl groups, i.e., xylitol. (The monosaccharide, erythrose, is not suitable in the practice of this invention since it only contains three hydroxyl groups; but the sugar alcohol derived from erythrose, i.e., erythritol, contains four hydroxyl groups and accordingly can be used.) Suitable five hydroxyl group-containing monosaccharides are galactose, fructose, and sorbose. Sugar alcohols containing six -OH groups derived from the hydrolysis products of sucrose, as well as glucose and sorbose, e.g., sorbitol, are also suitable. Examples of disaccharide polyols which can be used include maltose, lactose, and sucrose, all of which contain eight hydroxyl groups.

Preferred polyols for preparing the polyesters for use in the present invention are selected from the group consisting of erythritol, xylitol, sorbitol, glucose and sucrose. Sucrose is especially preferred.

The polyl starting material having at least four hydroxyl groups must be esterified on at least four of the -OH groups with a fatty acid containing from about 8 to about 22 carbon atoms. Examples of such fatty acids include caprylic, capric, lauric, myristic, myristoleic, palmitic, palmitoleic, stearic, oleic,
ricinoleic, linoleic, linolenic, eleostearic, arachidic, arachidonic, behenic, and erucic acid. The fatty acids can be derived from naturally occurring or synthetic fatty acids; they can be saturated or unsaturated, including positional and geometrical isomers, depending on the desired physical properties (e.g., liquid of a desired viscosity or solid) of the polyol fatty acid polyester compound being prepared.

Fatty acids per se or naturally occurring fats and oils can serve as the source for the fatty acid component in the polyol fatty acid polyester. For example, rapeseed oil provides a good source of C_{22} fatty acids. The C_{16}-C_{18} fatty acids can be obtained from tallow, soybean oil, and cottonseed oil. Shorter chain fatty acids can be obtained from coconut, palm kernel, and babassu oils. Corn oil, lard, oil, palm oil, peanut oil, safflower seed oil, sesame seed oil, and sunflower seed oil are examples of other natural oils which can serve as the course of the fatty acid used to prepare the polyesters herein.

Preferred fatty acids for preparing the polyol polyesters herein are the C_{14} to C_{18} acids, and are most preferably selected from the group consisting of myristic, palmitic, stearic, oleic, and linoleic fatty acids. Thus, natural fats and oils which have a high content of these fatty acids represent preferred sources for the fatty acid component, i.e., soybean oil, olive oil, cottonseed oil, corn oil, tallow and lard.

The polyol fatty acid polyesters useful in this invention must contain at least four fatty acid ester groups. Polyol fatty acid polyester compounds that contain three or less fatty acid ester groups are digested in and the products of digestion are absorbed from the intestinal tract much in the manner of ordinary triglyceride fats, whereas the polyol fatty acid polyester compounds that contain four or more fatty acid ester groups are substantially nondigestible and consequently nonabsorbable by the human body. It is not necessary that all of the hydroxyl groups of the polyol be esterified with fatty acid, but it is preferable that the polyester contain no more than two unesterified hydroxyl groups. Most preferably, substantially all of the hydroxyl groups of the polyol are esterified with fatty acid, i.e., the compound
is substantially completely esterified. The fatty acids esterified to the polyol molecule can be the same or mixed.

To illustrate the above points, a sucrose fatty triester would not be suitable for use herein because it does not contain the required four fatty acid ester groups. A sucrose tetra-fatty acid ester would be suitable, but is not preferred because it has more than two unesterified hydroxyl groups. A sucrose hexa-fatty acid ester would be preferred because it has no more than two unesterified hydroxyl groups. Highly preferred compounds in which all the hydroxyl groups are esterified with fatty acid include the sucrose octa-fatty acid esters.

In any given polyol fatty acid polyester compound the fatty acid ester groups can be selected on the basis of the desired physical properties of the compound. For example, the polyol polyesters which contain unsaturated fatty acid ester groups and/or a preponderance of short chain, e.g., C₁₂, fatty acid ester groups are generally liquid at room temperature. The polyols esterified with longer chain and/or saturated fatty acid groups such as stearoyl are solids at room temperatures.

The following are nonlimiting examples of specific polyol fatty acid polyesters containing at least four fatty acid ester groups suitable for use in the present invention: glucose tetraoleate, glucose tetrastearate, the glucose tetraesters of soybean oil fatty acids, the mannose tetraesters of mixed tallow fatty acids, the galactose tetraesters of olive oil fatty acids, the arabinose tetraesters of cottonseed oil fatty acids, xylose tetralinoleate, galactose pentastearate, sorbitol tetraoleate, the sorbitol hexaesters of olive oil fatty acids, xylitol pentapalmitate, the xylitol tetraesters of substantially completely hydrogenated cottonseed oil fatty acids, sucrose tetrastearate, sucrose pentastearate, sucrose hexaoleate, sucrose octaoleate, the sucrose octaesters of partially or substantially completely hydrogenated soybean oil fatty acids and the sucrose octaesters of peanut oil fatty acids.

As noted above, highly preferred polyol fatty acid esters are those wherein the fatty acids contain from about 14 to about 18 carbon atoms and are thus derived from such natural materials as soybean oil and olive oil. Examples of such compounds are the
erythritol tetraesters of olive oil fatty acids, erythritol tetraoleate, xylitol pentaoleate sorbitol hexaoleate, sucrose octaoleate, and the sucrose hexa-, hepta- and octaesters of soybean oil fatty acids, partially or substantially wholly hydrogenated.

The polyol fatty acid polyesters suitable for use herein can be prepared by a variety of methods well known to those skilled in the art. These methods include: transesterification of the polyol with methyl, ethyl or glycerol fatty acid esters using a variety of catalysts; acylation of the polyol with a fatty acid chloride; acylation of the polyol with a fatty acid anhydride; and acylation of the polyol with a fatty acid, per se. As an example, the preparation of polyol fatty acid esters is described in U.S. Patent 2,831,854, incorporated herein by reference. The most highly preferred methods of preparing the polyol polyesters used herein are disclosed in U.S. Patents 4,517,360 and 4,518,772, incorporated herein by reference.

Specific, but nonlimiting, examples of the preparation of polyol fatty acid esters suitable for use in the practice of this invention are as follows.

Erythritol tetraoleate - Erythritol and a five-fold molar excess of methyl oleate are heated at 180°C, under vacuum, with agitation, in the presence of sodium methoxide catalyst over two reaction periods of several hours each. The reaction product (predominately erythritol tetraoleate) is refined in petroleum ether and crystallized three times from several volumes of acetone at 1°C.

Xylitol pentaoleate - Xylitol and a five-fold molar excess of methyl oleate in dimethylacetamide (DMAC) solution are heated at 180°C for five hours in the presence of sodium methoxide catalyst, under vacuum. During this time the DMAC is removed by distillation. The product (predominately xylitol pentaoleate) is refined in petroleum ether solution and, after being freed of petroleum ether, is separated as a liquid layer four times from acetone at ca. 1°C and twice from alcohol at ca. 10°C.

Sorbitol hexaoleate is prepared by essentially the same procedure used to prepare xylitol pentaoleate except that sorbitol is substituted for xylitol.
Sucrose octaoleate is prepared by substantially the same procedure as that used to prepare erythritol tetraoleate except that sucrose is substituted for erythritol.

**Mixtures of Primary Agents** - It is to be understood that various of the aforesaid primary agents can be used herein conjointly. For example, the aryloxyisobutyric acids can be administered with psyllium. Likewise, the naphthenyl esters of 2-alkylbutanoic acids can be administered with polycationic resins. Likewise the aryloxy pentanoic acids can be administered with the aryloxyisobutyric acids. In particular, the conjoint administration of two or more of the primary agents selected from the classes of: (a) psyllium; (b) polycationic resins; and (c) polyol polyesters, is preferred. To illustrate this point, 10:1 to 1:10 (wt.), preferably 3:1 to 1:3, most preferably about 1:1 (wt.), binary mixtures of psyllium/cholesteramine,psyllium/polyol polyester, and cholesteramine/polyol polyester are quite useful herein. Likewise, ternary mixtures (typically about 1:1:1 to about 1:1:10, by wt.) of cholesteramine/psyllium/polyol polyester can also be used.

The fat-soluble vitamins can optionally be used to fortify the foregoing compositions. It will be appreciated that commercial preparations of the appropriate vitamins and/or appropriate vitamin mixtures which provide "fat-soluble" vitamins A, D, E and K can be used herein. See U.S. Patent 4,034,083 for details of the role of these vitamins in metabolism and their use in combination with polyesters of the type useful in this invention. The amount of the individual fat-soluble vitamins used to fortify the present compositions can vary with the age of the recipient, the dosage regimen used, and the amount of the vitamin ingested from other dietary sources.

II. **AGENTS FOR DECALCIFYING PLAQUE.**

Various sequestering, chelating and/or crystal growth modifying materials known in the pharmaceutical literature and safe for administration to living beings can be used herein to wholly or partially remove (or inhibit the deposition and/or crystal growth of) calcium in the vascular plaque. (The term "decalciify" herein is intended to include both the removal of calcium salts which are already deposited in mature plaque, as
well as the inhibition of further deposition of calcium and/or crystal growth in the plaque.) Reference can be made to standard formularies for such materials for use in the practice of this invention. However, since it is preferred that the invention herein be practiced by the oral administration of both the primary agent (above) and the auxiliary (decalcifying) agent, the attention of formulator will be primarily directed hereinafter to those types of auxiliary agents which can be absorbed from the gut into the bloodstream to provide their plaque-decalcifying effect in the blood vessels.

**Phosphonates** - The phosphonates comprise a class of calcium-affecting agents which are becoming well-known for use in disease states involving the anomalous mobilization and deposition of calcium in humans and lower animals. One such phosphonate currently in use is etidronic acid ([1-hydroxyethylidene]bisphosphonic acid, abb. "EHDP"), available under the trademark DIDRONEL. See Merck *ibid.* at 3819. EHDP is one of the geminal diphosphonates which, as a class, are preferred for use herein. It will be appreciated by those skilled in the art that various geminal, and vicinal phosphonates, triphosphonates, polyphosphonates, and the like, noted in the literature can also be used herein. Dichloromethane diphosphonate comprises one such material for use herein. Reference can be made to the patents cited above for various other examples of such phosphonates.

In more detail, of the preferred class of geminal diphosphonates herein the most preferred sub-class will also comprise a hydroxy group, i.e., the "hydroxy diphosphonates", which are compounds containing the moiety

![Chemical structure](image)

wherein M is typically H, a salt-forming cation (especially sodium) or an ester group. In the hydroxy diphosphonates, the fourth valence bond to the carbon atom depicted in the above formula will be filled by substituents such as hydrogen (hydroxymethyl diphosphonate, "HMDP"); alkyl substituents such as
methyl (EHDP); various cyclic alkyl, aryl and/or heteroaryl (especially pyridyl; see EP 186,405 cited above) substituents; substituted alkyl substituents, especially those wherein the substituting group is amino (e.g., the omega-amino-1-hydroxyalkylidene-1,1-bisphosphonates) and the like. Again, reference can be made to the patents cited above for various examples of such diphosphonates for use herein.

The diphosphonates can be used in the form of their acids, salts and esters. For purposes of illustration, with reference to the hydroxy diphosphate formula M can be H, a cation such as Na⁺, K⁺, NH₄⁺, and the like, or ester, e.g., -CH₃, -C₂H₅, etc. As noted, it is preferred to administer the phosphonates orally, so water-soluble salts, e.g., Na⁺, are generally preferred. However, phosphonates suitable for intramuscular and subcutaneous administration can comprise, for example, the amorphous calcium salts; see EP 444,405. Of the esters useful herein, the acyloxyethyl esters are of particular use, especially the pivaloyloxymethyl- and isobutanoxyloxymethyl-esters; see EP 416,689.

Other plaque decalcifying agents herein include the nitrilotriacetates, the citrates, the ethylenediaminetetraacetates (EDTA), various succinates and the like. Such agents generally fall within the class of "polycarboxylates". However, such polycarboxylate materials are much less preferred than the phosphonates, since many of them are not readily absorbed through the gut, although they can be administered by injection in sterile aqueous solution.

Treatment Regimen

It will be appreciated by the reader that the primary agents and auxiliary agents employed herein can be used at their respective generally recognized dosage levels to achieve the benefits afforded by the present invention. Dosage level information is available from a variety of published sources, such as the PHYSICIAN'S DESK REFERENCE, 46th Ed. (1992), Medical Economics Co., Inc. Montvale, NJ 07645. To illustrate this point, the oral administration of a primary agent such as MEVACOR which functions systemically will typically be at the 20-120 mg/day dose level, together with DIDRONEL (as the disodium salt) at the 5-20 mg/kg daily dose range. If selected as the primary
agent, LOPID is typically used at ca. 1,200 mg/day, administered in two dosages approximately 30 minutes before the morning and evening meals. Of course, matters such as age, weight, gender, blood lipid levels, etc., will be taken into consideration by the attending physician according to the needs of individual patients, and dosage levels adjusted accordingly.

For the primary agents which function nonsystemically, the same considerations as noted above apply. To illustrate usage of the nonsystemic primary agents, a typical treatment regimen comprises orally administering to the patient a safe and effective amount of psyllium seed gum, or source thereof, or cholestyramine, or a nonabsorbable, nondigestible polyol polyester of the type described hereinabove, or, conveniently, mixtures of two or three of these materials such as those illustrated hereinafter. Ingestion of from 1 g to 30 g of the psyllium material, or from 5 g to 40 g of the cholestyramine, or from 5 g to 50 g of the polyester material per day is appropriate in most circumstances. Since the psyllium material, the cholestyramine, and the polyol material are nontoxic and nonallergenic, even higher ingestion levels can be used without undue side effects. Daily ingestion is preferred, and a daily ingestion of from about 5 g to about 15 g of the psyllium material, or from about 12 g to about 32 g of the cholestyramine, or from about 15 g to about 50 g of the polyester material is most commonly used, with said ingestion being portion-wise at two, three or four regularly spaced intervals throughout the day. Again, depending on the patient’s size and cholesterol level in the patient’s blood, this can be varied. Administration just before meals and at bedtime is convenient. Smaller dosages of the individual materials can be used if they are employed conjointly.

As mentioned, it is convenient to use the psyllium and the cholestyramine and, optionally, the polyester, as a mixture. By way of illustration and not limitation, cholestyramine is admixed with the psyllium, generally in a weight ratio of about 10:1 to about 1:10, preferably 3:1 to 1:3, conveniently 1:1. These materials are powders and readily admix. If a polyester is used, it can be employed at a weight ratio (polyester:mixed psyllium/cholestyramine) from 10:1 to 1:10, preferably 3:1 to 1:3,
conveniently 1:1. When a liquid polyester such as sucrose octaoleate is used at a weight ratio of 1:1, the resulting ternary mixed composition has the appearance of resinous granules. These granules can be compacted to provide tablets or capsules, or, conveniently, can be spooned-out from the bulk mixture and either administered by the spoonful or admixed with water and drunk. Binary mixtures of polyester with either psyllium or cholestyramine at a 10:1 to 1:10 ratio can also be employed, but ternary mixtures are more effective.

The following Examples further illustrate the practice of this invention.

**EXAMPLE I**

The following compositions are provided by simply admixing the indicated ingredients. The mixtures can be individually packaged in individual dosage units, or can be provided in bulk form.

**MIXTURE A**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psyllium (as blond psyllium husk, macerated)</td>
<td>3.8 g</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>3.8 g</td>
</tr>
<tr>
<td>Ethane-1-Hydroxy-1,1-Diphosphonate (as sodium salt)</td>
<td>60 mg</td>
</tr>
</tbody>
</table>

The ingredients are dry-blended to form a unit dose composition. Three such unit dosages are ingested daily, typically in water at mealtimes, or according to the instructions of the attending physician.

**MIXTURE B**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Amino-1-Hydroxybutyrate</td>
<td>100 mg</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>15 mg</td>
</tr>
</tbody>
</table>

The ingredients are dry-blended and pressed in a standard tablet press using conventional excipients and tableting aids. The tablets are administered orally, twice daily at mealtimes, or according to the instructions of the attending physician.

**MIXTURE C**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1-Hydroxy-2-(3-Pyridinyl)Ethylidene]bis</td>
<td>70 mg</td>
</tr>
<tr>
<td>[Phosphonic Acid] Monosodium salt</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

SUBSTITUTE SHEET
A dry blend of the powdered ingredients are formed into tablets or capsules by conventional techniques. Administration is by oral ingestion, two or three times daily, or according to the instructions of the attending physician.

**MIXTURE D**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Amino-1-Hydroxyhexane-1,1-Diphosphonic Acid</td>
<td>100 mg</td>
</tr>
<tr>
<td>(as Na salt)</td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>25 mg</td>
</tr>
</tbody>
</table>

A dry blend of the powdered ingredients is prepared and tableted using a conventional tablet press. Typical administration is by oral ingestion, two or three times daily, or according to the instructions of the attending physician.

**MIXTURE E**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine</td>
<td>5 g</td>
</tr>
<tr>
<td>Nitrilotriacetate (Na salt)</td>
<td>1 g</td>
</tr>
<tr>
<td>Psyllium</td>
<td>5 g</td>
</tr>
</tbody>
</table>

The ingredients are dry-blended. The resulting powder is dispersed in 250 ml water for oral ingestion. Oral ingestion is typically on a twice-daily basis, or according to the instructions of the attending physician.

**MIXTURE F**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colestipol</td>
<td>3 g</td>
</tr>
<tr>
<td>Sucrose Octaoleate</td>
<td>20 g</td>
</tr>
<tr>
<td>Sodium EDTA</td>
<td>1 g</td>
</tr>
</tbody>
</table>

The ingredients are blended and administered orally, twice daily, for a period of 60 days.

**MIXTURE G**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemfibrozil</td>
<td>100 mg</td>
</tr>
<tr>
<td>Hydroxyxymethanediphosphonate, Na Salt</td>
<td>200 mg</td>
</tr>
</tbody>
</table>

A dry blend of the ingredients is prepared and tableted. Typical administration is by oral ingestion, twice daily, for 60 days.
MIXTURE H

Ingredient                          Amount  
Clofibrate                          200 mg  
6-Amino-1-Hydroxyhexane-1,1-Diphosphonate, Na Salt  100 mg  
A dry blend of the ingredients is prepared and administered orally, twice daily.

EXAMPLE II

Kits comprising individual unit doses of the primary agent and auxiliary agent herein are provided, as follows. Conveniently such kits can readily be assembled to supply sufficient quantities of both the primary and the auxiliary agents for about 30 days’ treatment. Accordingly, in the following kits, 60 tablets of each of the agents are provided, thereby allowing the patient to orally ingest one tablet of each agent twice daily over the 30-day lifetime of a single kit. Thereafter, further kits can be secured by the patient, as may be determined by the attending physician, to extend the period of treatment.

The treatment regimen can comprise orally ingesting both the primary agent and the auxiliary agent, concurrently. In the alternative, in some patients it can be useful to ingest the two types of agents sequentially, in what might be termed a "split" treatment regimen. To illustrate this point, in a split treatment regimen the calcium-affecting auxiliary agent can be administered for an initiation period, typically 30-90 days, to partially decalcify the plaque; thereafter, the primary agent is administered to diminish or remove the vesicular plaque deposit. Variations on the concurrent treatment and split treatment regimens can also be used, and it will be appreciated that the kits described below will be convenient and easy to use, whatever regimen is employed.

**Tablets**

<table>
<thead>
<tr>
<th>Kit</th>
<th>Dosage per Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT 1</td>
<td></td>
</tr>
<tr>
<td>EHDP (as DIDRONEL)</td>
<td>200 mg</td>
</tr>
<tr>
<td>Lovastatin (as MEVACOR)</td>
<td>20 mg</td>
</tr>
<tr>
<td>KIT 2</td>
<td></td>
</tr>
<tr>
<td>EHDP (as DIDRONEL)</td>
<td>400 mg</td>
</tr>
<tr>
<td>Gemfibrozil (as LOPID)</td>
<td>600 mg</td>
</tr>
<tr>
<td>Kit</td>
<td>Ingredients</td>
</tr>
<tr>
<td>-----</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>KIT 3</td>
<td>EHDP (as DIDRONEL)</td>
</tr>
<tr>
<td></td>
<td>Clofibrate</td>
</tr>
<tr>
<td>KIT 4</td>
<td>Lovastatin (MEVACOR)</td>
</tr>
<tr>
<td></td>
<td>6-Amino-1-Hydroxyhexane-1,1-Diphosphonate, Na</td>
</tr>
<tr>
<td>KIT 5</td>
<td>Nitrilotriacetate, Na</td>
</tr>
<tr>
<td></td>
<td>Gemfibrozil (as LOPID)</td>
</tr>
</tbody>
</table>

The following kits provide individually packaged unit dosages of non-systemic auxiliary agents and tablets of primary agents. The weights shown are weights of indicated ingredients per packet and per table, respectively. Typically, the packeted auxiliary agent is dispersed in water prior to oral ingestion.

**KIT 6**

1:1 Mixture Cholestyramine/Psyllium | 10 g  
EHDP Tablets (as DIDRONEL) | 400 mg  

**KIT 7**

1:1 Mixture Cholestyramine/Psyllium | 10 g  
6-Amino-1-Hydroxyhexane-1,1-Diphosphonate, Na Tablets | 150 mg  

**KIT 8**

1:1 Mixture Cholestyramine/Psyllium | 15 g  

**KIT 9**

Psyllium (as METAMUCIL) | 20 g  
Dichloromethane Diphosphonate, Na Tablets | 150 mg  

**KIT 10**

Psyllium (as METAMUCIL) | 15 g  
(2-Pyridyl)Methane Diphosphonic Acid Tablets | 150 mg  

**KIT 11**

1:1:5 (wt.) Mixture Cholestyramine/Psyllium/ Sucrose Octaoleate | 20 g  
EHDP (as DIDRONEL) | 200 mg  

**KIT 12**

1:2 (wt.) Mixture Cholestyramine/METAMUCIL | 20 g  
Nitrilotriacetate, Na Tablets | 400 mg  

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KIT 13

1:2 (wt.) Mixture Cholestyramine/METAMUCIL 20 g
Sodium Citrate Tablets 200 mg

The foregoing examples illustrate the preferred mode of treatment herein, which comprises oral ingestion of a non-phosphonate primary agent and a phosphonate or (less preferred) carboxylate auxiliary agent. The following example illustrates a different mode of administration.

EXAMPLE III

A sterile aqueous suspension of the amorphous insoluble calcium salt of (4-amino-1-hydroxybutyridene)-1,1-bisphosphonic acid is prepared according to the teaching of EP 449 405 at a concentration of 20 mg P/ml. 5 mls of the suspension are injected by hypodermic into the hip of an atherosclerotic patient. The patient is concurrently placed on a regimen of oral ingestion of Lovastatin (as MEVACOR), as 40 mg tablets ingested twice daily before morning and evening meals, for a period of 30 days. The treatment regimen may be repeated, as required.

The foregoing illustrates the practice of this invention using various dosage levels. To illustrate this further, and not by way of limitation, typical dosage levels of the systemic primary agents will range from about 5 mg/day to about 2000 mg/day. Dosages of the non-systemic agents will range from about 1 g to about 100 g per day. Dosages of the auxiliary agent will range from about 1 mg/kg body weight to about 200 mg/kg body weight per day.

As noted hereinabove, the method and compositions of the present invention can be fortified with one or more vitamins. The vitamins listed hereinabove are the type generally listed as "fat-soluble" vitamins, but water-soluble vitamins such as the B-complex vitamins (e.g., thiamine, riboflavin, nicotinic acid, pyridoxine, pantothenic acid, biotin, choline, inositol, p-aminobenzoic acid, cyanocobalamine), Vitamin A (including A1, retinoic acid and A2 3-dehydrotretinol, and especially Vitamin C (ascorbic acid) can also be employed. Mixtures of such vitamins, e.g., mixtures of Vitamins C and E; mixtures of B vitamins and D; mixtures of Vitamins A, C and E, and the like, can be employed. It is to be noted that use of such vitamins herein is not simply
to impart a nutritional benefit to the compositions. Rather, the vitamins, especially those which have an "antioxidative effect", especially Vitamin E, Vitamin C, and mixtures thereof, impart additional anti-atherosclerotic benefits when used in combination with the primary-plus-auxiliary agents employed in the practice of the invention herein. Thus, tripartite compositions and/or treatment regimens employing the primary agent, the auxiliary agent, and one or more vitamins or combinations of vitamins are provided by the invention. While not intending to be limited by theory, it would appear that the use of vitamins in the practice of this invention could function to provide additional anti-atherosclerotic benefits in the following way. Calcified plaque is decalcified by means of the auxiliary agent and plaque removal is afforded by mass action and/or solubilization phenomena when the total blood cholesterol level is lowered by means of the primary agent. Current theory holds that even residual amounts of cholesterol can oxidize and re-form plaque, especially if the patient is predisposed to plaque formation by genetic or other conditions. However, on speculation, it is believed that the presence of the vitamins, especially the antioxidation vitamins, prevents oxidation of these residual amounts of blood cholesterol and thereby inhibits its redeposition as a new atherosclerotic plaque. Whatever the mode of action, the use of vitamins in combination with the other ingredients herein is fully contemplated by this invention. The following Examples further illustrate this point.

Usage levels of the vitamins in the following Examples are given for purposes of illustration and not by way of limitation. Vitamins are usually administered in recommended daily allowances (RDA) or multiples thereof. The formulator can refer to standard tables for RDA values for each of the vitamins. Dosages can range as high as 30 mg three times daily (e.g., for thiamine). However, the so-called "mega-dosages" of vitamins are also becoming commonplace, and dosage amounts of up to several grams per day of vitamins such as Vitamin C are reported. In general, then, the amount of vitamin used herein (either fat-soluble, water-soluble or both) will typically range from about 0.1 mg to about 5 g per day, preferably from about 1 RDA to about 10 RDA per day.
EXAMPLE IV

Kits are provided in the manner of Example II by the addition of vitamin tablets to KITS 1-13, as follows: KITS 1 and 8 - Vitamin C 500 mg tablets; KITS 2 and 9 - Vitamin C 1,000 mg tablets; KITS 3 and 10 - Vitamin C 1,000 mg tablets/Vitamin E tablets 1,000 International Units of vitamin; KITS 4 and 11 - Vitamin B complex 1,000 mg tablets/500 mg tablets Vitamin C; KITS 5 and 12 - Vitamin B 30 mg tablets/Vitamin D 200 mg tablets; KITS 6 and 13 - Vitamins A, B, C and E as multivitamin tablets comprising 1 RDA of each vitamin; KIT 7 - Vitamin C 250 mg tablets. In-use, one of each of the indicated vitamin tablets is ingested each time the primary agent and/or the auxiliary agent is ingested. Thus, if the primary agent and auxiliary agent are ingested concurrently, one of each of the vitamin tablets is also ingested concurrently. If the "split" treatment regimen of Example II is employed, the vitamins are ingested with the agent given in each leg of the treatment.

EXAMPLE V

The MIXTURES of Examples I A through H are each "vitaminized" by the addition of 750 mg Vitamin C and 500 mg Vitamin E and ingested in the manner indicated.

EXAMPLE VI

The treatment regimen of Example III is modified by the concurrent daily administration of a multivitamin tablet comprising at least one RDA of each of the above-noted fat-soluble and water-soluble vitamins.

EXAMPLE VII

In an alternate mode, the compositions and methods herein are modified by administering from about 50 mg to about 1,000 mg, preferably 100 mg to 500 mg of acetylsalicylic acid (aspirin) per day to the patient to provide additional benefits associated with the ability of the aspirin to decrease platelet aggregation and otherwise benefit the overall vascular health of the affected patient.
What is claimed is:

1. The use of a primary agent which reduces plaque and an auxiliary agent which decalcifies plaque in an improved method for reducing atherosclerotic plaque build-up in the blood vessels of a human or animal patient in need of such treatment, characterized in that said improved method is comprised of administering to said patient one or more primary agents which safely and effectively reduce a plaque-producing member selected from the group consisting of cholesterol; LDL triglycerides; total plasma triglycerides, or mixtures thereof, in said patient, further characterized in that the improvement comprises additionally administering to said patient an amount of an auxiliary agent which wholly or partially decalcifies said plaque.

2. A method according to Claim 1 wherein said primary agent is a member selected from the group consisting of the aryloxyisobutyric acids; the arylxoxypentanoic acids; the substituted naphthalenyl esters of 2-alkylbutanoic acid; polycationic resins; psyllium; and nonabsorbable, nondigestible polyol polyesters; and preferably, the substituted naphthalenyl esters of 2-alkyl butanoic acid; polycationic resins; psyllium; and nonabsorbable, nondigestible polyol polyesters and mixtures thereof.

3. A method according to Claim 1 wherein said auxiliary agent is a member selected from the group consisting of the nitrilotriacetates; the geminal diphosphonates; the vicinal di- or poly-phosphonates; and mixtures thereof; preferably a geminal diphosphonate containing at least one hydroxy-substituted diphosphonate moiety.

4. A composition of matter for reducing atherosclerotic plaque, characterized in that it comprises a mixture of a safe and effective amount of:
(a) one or more primary agents which safely and effectively reduce a plaque-producing member selected from the group consisting of cholesterol, LDL triglycerides, total plasma triglycerides, or mixtures thereof; and

(b) an auxiliary agent which wholly or partially decalcifies said plaque.

5. A composition according to Claim 4 wherein said primary agent is a member selected from the group consisting of the aryloxyisobutyric acids; the aryloxypentanoic acids; the substituted naphthalenyl esters of 2-alkylbutanoic acid; polycationic resins; psyllium; and nonabsorbable; nondigestible polyol polyesters; and mixtures thereof; and preferably, the substituted naphthalenyl esters of 2-alkyl butanoic acid; polycationic resins; psyllium; nonabsorbable, and nondigestible polyol polyesters and mixtures thereof.

6. A composition according to Claim 4 wherein said auxiliary agent is a member selected from the group consisting of the nitrilotriacetates; the geminal diphosphonates; the vicinal di- or poly-phosphonates; and mixtures thereof; and preferably a geminal diphosphonate containing at least one hydroxy-substituted diphosphonate moiety.

7. A pharmaceutical composition in kit form for reducing atherosclerotic plaque characterized in that it comprises individual unit doses of:

(a) one or more primary agents which safely and effectively reduce a plaque-producing member selected from the group consisting of cholesterol, LDL triglycerides, total plasma triglycerides, or mixtures thereof; and

(b) an auxiliary agent which wholly or partially decalcifies said plaque.

8. A kit according to Claim 7 wherein said primary agent is a member selected from the group consisting of the
aryloxyisobutyric acids; the aroyloxypentanoic acids; the
substituted naphthalenyl esters of 2-alkylbutanoic acid;
polycationic resins; psyllium; and nonabsorbable, nondigestible
polyl polyesters; and mixtures thereof; and preferably, the sub-
stituted naphthalenyl esters of 2-alkyl butanoic acid;
polycationic resins; psyllium; and nonabsorbable, nondigestible
polyl polyesters and mixtures thereof.

9. A kit according to Claim 7 wherein said auxiliary agent is a
member selected from the group consisting of the nitrilotriace-
tates; the geminal diphosphonates; the vicinal di- or poly-
phosphonates; and mixtures thereof, preferably a geminal
diphosphonate containing at least one hydroxy-substituted
diphosphonate moiety.

10. A method according to Claim 1 which additionally comprises
administration of aspirin and one or more vitamins to the
patient, preferably Vitamin C, Vitamin E and mixtures thereof.
<table>
<thead>
<tr>
<th>I. CLASSIFICATION OF SUBJECT MATTER</th>
<th>(if several classification symbols apply, indicate all)</th>
</tr>
</thead>
<tbody>
<tr>
<td>According to International Patent Classification (IPC) or to both National Classification and IPC</td>
<td></td>
</tr>
<tr>
<td>Int.Cl. 5 A61K45/06; A61K35/78; A61K31/785; A61K31/365</td>
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<tr>
<td>II. FIELDS SEARCHED</td>
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<tr>
<td>Classification System</td>
<td>Minimum Documentation Searched7 Classification Symbols</td>
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<tr>
<td>Int.Cl. 5</td>
<td>A61K</td>
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<td>LEHerte C.F.M.</td>
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INTERNATIONAL SEARCH REPORT
International Application No PCT/US 93/00332 -2-

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)

According to International Patent Classification (IPC) or to both National Classification and IPC


II. FIELDS SEARCHED

Minimum Documentation Searched

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III. DOCUMENTS CONSIDERED TO BE RELEVANT

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* Special categories of cited documents:
   - "A": document defining the general state of the art which is not considered to be of particular relevance
   - "E": earlier document but published on or after the international filing date
   - "L": document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
   - "O": document referring to an oral disclosure, use, exhibition or other means
   - "P": document published prior to the international filing date but later than the priority date claimed

* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

*"X": document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

*"Y": document of particular relevance; the claimed invention cannot be considered novel if the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

*"&": document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

Date of Mailing of this International Search Report

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

Form PCT/ISA/210 (second sheet) (January 1985)
**INTERNATIONAL SEARCH REPORT**

**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
   REMARK: Although claims 1-3 are directed to a method of treatment of ANIMAL (diagnostic method practised on) the human body the search has been carried out and based on the alleged effects of the compound/composition.

2. **☐** Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. **☐** Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. **☐** As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. **☐** As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- **☐** The additional search fees were accompanied by the applicant’s protest.
- **☐** No protest accompanied the payment of additional search fees.
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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 29/04/93

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