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SUPERINDUSTRIA Y COMERCIO

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DIVISION DE NUEVAS CREACIONES

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REF: Expediente No. 02 089.167 - Solicitud de Patente FASE NACIONAL
a nombre de ASTRAZENECA AB Titulada: NUEVA COMBINACIÓN
DE UN BETA-BLOQUEADOR Y UN AGENTE QUE REDUCE EL
COLESTEROL

RAMIRO CASTRO DUQUE, vecino de Bogotá, portador de la tarjeta profesional No. 1003, obrando como apoderado de la Sociedad ASTRAZENECA AB, según lo acredita el documento de Poder presentado en esa División, me permito anexar al presente escrito los siguientes documentos:

1. Copia certificada por la Oficina de Patentes de Suecia, de la primera solicitud presentada para la misma invención, de la cual REIVINDICAMOS PRIORIDAD.

De la señora jefe atentamente,



RAMIRO CASTRO DUQUE

C.C. No. 170.322 de Bogotá

Código 340

Cra 7a. No. 16-56 Piso 9

Bogotá, Abril 16, 2003

CPB/hsr

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PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

Intyg Certificate

Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

Ansökan ingavs ursprungligen på engelska.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

The application was originally filed in English.

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62**NEW COMBINATION****FIELD OF THE INVENTION**

5 The present invention relates to pharmaceutical formulations a betablocker and a cholesterol-lowering agent in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, as well as a kit of parts, a method for treatment and use of the formu-
lations for the prophylactic or therapeutic treatment of atherosclerosis, particularly in
patients suffering from hyperlipidemia, including hypercholesterolemia.

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BACKGROUND OF THE INVENTION

There is a constant need for new medications to further reduce the risk of atherosclerotic
disease. This is especially true for patient populations at a higher risk than the population at
15 large, e.g. patients suffering from hypercholesterolemia and hyperlipoproteinemia.

Various pharmaceuticals, such as the group known as statins, are known to lower the
concentration of total serum cholesterol as well as influence the ratio between the
concentration of the positive high-density lipid (HDL) cholesterol and the negative low-
20 density lipid (LDL) cholesterol.

Betablockers on the other hand are known to have a positive influence on various cardio-
vascular disease, primarily hypertension, whereas the effect upon atherosclerotic disease is
little known.

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The combination of betablockers and cholesterol-lowering agents at large has not been
disclosed previously, and particularly not for the prophylactic and therapeutic treatment of
patients suffering from, or susceptible to, atherosclerosis, hypercholesterolemia or
hyperlipoproteinemia.

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SUMMARY OF THE INVENTION

The present invention relates to pharmaceutical combinations containing a betablocker and a cholesterol-lowering agent, pharmaceutical formulations containing a betablocker and a
5 cholesterol-lowering agent in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, as well as a method for treatment and use of the formulations for the prophylactic or therapeutic treatment of atherosclerosis, hypercholesterolemia and hyperlipoproteinemia.

10 The invention further relates to a kit of parts of vessels containing the betablocker and the cholesterol-lowering agent and instructions for the administration of the betablocker and cholesterol-lowering agent to a patient in need thereof.

The invention also relates to a kit of parts of formulations containing the betablocker and
15 the cholesterol-lowering agent each in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

DETAILED DESCRIPTION OF THE INVENTION

20 It has surprisingly been found that, compared to the separate use of a betablocker and a cholesterol-lowering agent, the present invention comprising a combination of a betablocker and a cholesterol-lowering agent has an anti-atherosclerotic effect, particularly in patients suffering from hypercholesterolemia or hyperlipoproteinemia.

25 In one aspect, the present invention thus relates to pharmaceutical combinations, comprising a betablocker and a cholesterol-lowering agent.

In another aspect, the present invention relates to pharmaceutical formulations, comprising:
a betablocker and a cholesterol-lowering agent in admixture with a pharmaceutically
30 acceptable adjuvant, diluent or carrier.

A further aspect of the present invention relates to kits of parts comprising:

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(i) a vessel containing a betablocker and
(ii) a vessel containing a cholesterol-lowering agent,
and instructions for the simultaneous, separate or sequential administration of the
betablocker and cholesterol-lowering agent to a patient in need thereof.

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Another aspect of the invention relates to kits of parts comprising:

(i) a pharmaceutical formulation containing a betablocker in admixture with a
pharmaceutically acceptable adjuvant, diluent or carrier; and
(ii) a pharmaceutical formulation containing a cholesterol-lowering agent in admixture
10 with a pharmaceutically acceptable adjuvant, diluent or carrier;
which betablocker and cholesterol-lowering agent are each provided in a form that is
suitable for administration in conjunction with the other.

By "administration in conjunction with", we include that respective formulations
15 comprising a betablocker and a cholesterol-lowering agent are administered,
simultaneously, separately or sequentially, over the course of treatment of the relevant
condition, which condition may be acute or chronic. Particularly, the term includes that the
two formulations are administered (optionally repeatedly) sufficiently closely in time for
there to be a beneficial effect for the patient, that is greater, over the course of the treat-
20 ment of the relevant condition, than if either of the two formulations are administered
(optionally repeatedly) alone, in the absence of the other formulation, over the same course
of treatment. Determination of whether a combination provides a greater beneficial effect
in respect of, and over the course of treatment of, a particular condition, will depend upon
the condition to be treated or prevented, but may be achieved routinely by the person
25 skilled in the art.

Thus, the term "in conjunction with" includes that one or other of the two formulations
may be administered (optionally repeatedly) prior to, after, or at the same time as,
administration with the other component. When used in this context, the terms "admini-
30 stered simultaneously" and "administered at the same time as" include that individual
doses of a betablocker and a cholesterol-lowering agent are administered within 48 hours,
e.g. 24 hours, of each other.

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Yet another aspect of the invention relates to methods for prophylactic or therapeutic treatment of a patient suffering from, or susceptible to, atherosclerosis, which method comprises administering to the patient a therapeutically effective total amount of

- 5 (i) a betablocker in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; in conjunction with
(ii) a cholesterol-lowering agent in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

- 10 Still another aspect of the invention relates to methods for prophylactic or therapeutic treatment of a patient suffering from, or susceptible to, atherosclerosis, which method comprises administering to the patient a pharmaceutical formulation, comprising:

- (i) a betablocker and
(ii) a cholesterol-lowering agent in
15 admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

A still further aspect of the invention relates to the use of pharmaceutical formulations, comprising:

- (i) a betablocker and
20 (ii) a cholesterol-lowering agent in
admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,
in the manufacture of a medicament for the prophylactic or therapeutic treatment of atherosclerosis.

25 Betablockers

- The betablockers referred to in this application include but are not limited to the compounds selected from the group consisting of acebutolol, alprenolol, amosulalol, arotinolol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucumolol,
30 bufetolol, bufuralol, bunitrolol, buprandolol, butofilolol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, cloranolol, dilevalol, epanolol, indenolol, labetalol, levobumolol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivalol, nipradilol,

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oxprenolol, perbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sufinalol, talindol, tertatolol, tilisolol, timolol, toliprolol, and xibenolol, and pharmaceutically acceptable salts or solvates thereof, or solvates of such salts.

- 5 In the present invention the betablocker is suitably metoprolol or atenolol or pharmaceutically acceptable salts or solvates thereof, or solvates of such salts. Particularly, the betablocker is metoprolol succinate (disclosed in US 5,001,161) or metoprolol tartrate.

- 10 In the present application, the term "betablocker" include chemical modifications, such as esters, prodrugs and metabolites, whether active or inactive, and pharmaceutically acceptable salts or solvates of any of these, or solvates of such salts.

Cholesterol-lowering agents

- 15 The cholesterol-lowering agents referred to in this application include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin selected from the group consisting of atorvastatin, cerivastatin, lovastatin, nivistatin, pravastatin and simvastatin. Particularly preferred statins are, however, fluvastatin (disclosed in European Patent Application, Publication No. EP-A-0114027), or a pharmaceutically acceptable salt, especially sodium, or solvate thereof, or a solvate of such a salt, and a compound with the chemical formula (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt. The compound (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl-(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, and its calcium and sodium salts are disclosed in European Patent Application, Publication No. EP-A-0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444.
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- 30 In the present application, the term "cholesterol-lowering agent" include chemical modifications, such as esters, prodrugs and metabolites, whether active or inactive, and pharmaceutically acceptable salts or solvates of any of these, or solvates of such salts.

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67**Pharmaceutical formulations**

The present invention relates to pharmaceutical compositions containing a betablocker and
5 a cholesterol-lowering agent as active ingredients.

Preferred combinations of a betablocker and a cholesterol-lowering agent are those where
the betablocker is metoprolol or atenolol, particularly metoprolol succinate or metoprolol
tartrate, and the cholesterol-lowering agent is a statin, particularly fluvastatin or a
10 compound with the chemical formula (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-
[methyl(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid,
or a pharmaceutically acceptable salt, especially the calcium and sodium salts, or solvate
thereof, or a solvate of such a salt.

15 In the present invention, the formulation and/or kits of parts may comprise two or more
betablockers in combination with a cholesterol-lowering agent, two or more cholesterol-
lowering agents in combination with a betablocker or any combination thereof.

For clinical use, the betablocker and the cholesterol-lowering agent are formulated into a
20 pharmaceutical formulation for oral, intravenous, subcutaneous, tracheal, bronchial,
intranasal, pulmonary, transdermal, buccal, rectal, parenteral or some other mode of
administration. The pharmaceutical formulation contains the betablocker and the
cholesterol-lowering agent in admixture with a pharmaceutically acceptable adjuvant,
diluent or carrier.

25 The total amount of active ingredients suitably is in the range of from about 0.1 % (w/w) to
about 95 % (w/w) of the formulation, suitably from 0.5 % to 50 % (w/w) and particularly
from 1 % to 25 % (w/w).

30 The molar ratio between the betablocker and the cholesterol-lowering agent may be in the
range of from about 1000:1 to about 1:1000. The molar ratio between the betablocker and

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the cholesterol-lowering agent lies suitably in the range of from 300:1 to 1:300, and particularly from 50:1 to 1:50.

In the preparation of the pharmaceutical formulations of the present invention the active ingredients may be mixed with solid, powdered ingredients, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture may then be processed into granules or pressed into tablets.

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The active ingredients may be separately premixed with the other non-active ingredients, before being mixed to form a formulation. The active ingredients may also be mixed with each other, before being mixed with the non-active ingredients to form a formulation.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active ingredients of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Hard gelatine capsules may contain granules of the active ingredients. Hard gelatine capsules may also contain the active ingredients in combination with solid powdered ingredients such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatine.

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Dosage units for rectal administration may be prepared (i) in the form of suppositories which contain the active substance mixed with a neutral fat base; (ii) in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules; (iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

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Liquid preparations may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing the active ingredients and the remainder consisting, for example, of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain coloring agents,

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flavoring agents, preservatives, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

5 Solutions for parenteral administration may be prepared as a solution of a formulation of the invention in a pharmaceutically acceptable solvent. These solutions may also contain stabilizing ingredients, preservatives and/or buffering ingredients. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent before use.

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The dose of the compound to be administered will depend on the relevant indication, the age, weight and sex of the patient and may be determined by a physician. The dosage will particularly be in the range of from 0.01 mg/kg to 10 mg/kg.

15 The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, the route of administration, the age, weight and sex of the patient and may be determined by a physician. In general, oral and parenteral dosages will be in the range of 0.1 to 1,000 mg per day of total active ingredients.

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In the present invention, "a therapeutically effective total amount" relates to a total amount of the a betablocker and the cholesterol-lowering agent which when given in combination gives a therapeutic effect, even though each amount when given separately may be less than the therapeutically effective amount.

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Medical and pharmaceutical use

Also provided according to the present invention are formulations and kits of parts for use in medical therapy; the use of formulations of the present invention in the manufacture of
30 medicaments for use in the prophylactic or therapeutic treatment of atherosclerosis, and methods of medical treatment or prophylaxis comprising the administration of a therapeu-

tically effective total amount of a betablocker and a cholesterol-lowering agent to a patient suffering from, or susceptible to, atherosclerosis.

The betablocker and the cholesterol-lowering agent can be administered as a combined preparation for simultaneous, separate or sequential use in atherosclerosis therapy. Furthermore, the betablocker can be administered prior to the administration of the cholesterol-lowering agent or vice versa.

The term 'medical therapy' as used herein is intended to include prophylactic, diagnostic and therapeutic regimens carried out in vivo or ex vivo on humans or other mammals.

The formulations of the invention are expected to be useful in prophylactic or therapeutic treatment of atherosclerosis, particularly in patients suffering from, or susceptible to hyperlipoproteinemia, and in particular hypercholesterolemia.

The formulations of the invention are furthermore expected to be useful in prophylactic or therapeutic treatment of cardiovascular complications in general, including, but not limited to, congestive heart failure (CHF), myocardial infarction (MI) including acute myocardial infarction (AMI), stroke, and mortality.

The following Example is intended to illustrate, but in no way limit the scope of the invention.

EXAMPLE

A large-scale clinical trial was designed to examine the effect of the betablocker metoprolol in combination therapy with a cholesterol-lowering agent versus placebo (only cholesterol-lowering agent). The study was a three-year prospective, randomised, placebo controlled, double blind pilot study in order to evaluate the effect of the combination of metoprolol and a cholesterol-lowering agent on atherosclerosis development in the carotid and femoral arteries.

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The inclusion criteria were willingness to participate, 20-70 years of age, serum cholesterol > 6.5 mmol/L, low density lipid (LPL) cholesterol > 5.0 mmol/L, and serum triglycerides < 4.5 mmol/L.

5 One hundred twenty-nine patients were randomised to the study, 62 to the combination treatment and 67 to placebo. The total number of patients after run-in was one hundred and three patients, 47 in the combination group and 56 in the placebo group. Seventy-nine patients completed the study, 35 in the combination group and 44 in the placebo group.

10 During the study, 39 patients in the placebo group were treated with a statin, mean dose 17.1 mg, and 33 patients in the combination group, mean dose 19.0 mg (n.s.). During the study, thirteen patients in the placebo group were given cholestyramine, mean dose 11,282 mg, and nine patients in the combination group, mean dose 16,148 mg.

15 Of the seventy-nine patients completing the study, 35 out of 35 in the combination group and 42 out of 44 in the placebo group were on a simultaneous cholesterol-lowering treatment.

20 The distribution of males and females in the groups were similar, 18 and 22 males and 17 and 22 females in the combination and placebo group, respectively. Likewise, the mean age was 60.6 and 59.6 for the combination and placebo group, respectively.

The mean time of follow-up was 2.97 years.

25 The results of the measurements of the lipid levels including cholesterol are evident from Table I.

The three values in each box are the baseline value, the result after three-year follow-up and the difference therebetween given as mean $\pm$ standard deviation (SD).

TABLE I

Characteristics	Combination therapy (n = 35)	Placebo (n = 44)	p-value for difference between groups during follow-up
Total serum cholesterol (mmol)	9.39 ± 2.42 6.01 ± 1.19 - 3.38 ± 2.10	9.39 ± 2.42 6.22 ± 1.08 - 2.44 ± 1.79	p < 0.05
HDL cholesterol (mmol)	1.42 ± 0.33 1.39 ± 0.40 - 0.03 ± 0.32	1.27 ± 0.37 1.39 ± 0.37 0.12 ± 0.17	p < 0.05
LDL cholesterol (mmol)	7.28 ± 2.46 4.08 ± 1.13 - 3.20 ± 2.07	6.74 ± 1.91 4.21 ± 1.10 - 2.53 ± 1.81	n.s.
Serum triglycerides (mmol/L)	1.87 ± 0.92 1.84 ± 0.88 - 0.03 ± 0.97	2.11 ± 0.80 1.99 ± 0.81 - 0.12 ± 0.79	n.s.
Systolic blood pressure (mm Hg)	138 ± 19 132 ± 16 - 6 ± 14	137 ± 21 135 ± 21 - 2 ± 16	n.s.
Diastolic blood pressure (mm Hg)	80 ± 6 77 ± 8 - 3 ± 9	80 ± 7 78 ± 8 - 2 ± 8	n.s.
Heart rate (bpm)	71 ± 10 64 ± 9 - 7 ± 12	71 ± 11 69 ± 10 - 2 ± 11	p < 0.05

It is evident from Table I, that after the three-year follow-up significant differences could be observed between the groups as regards total serum cholesterol, high density lipid

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(HDL) cholesterol and heart rate. These differences are statistically significant ($p < 0.05$ in all three variables).

The results of the intima-media thickness (IMT) and lumen diameter (LD) measurements
5 are evident from Table II.

The intima-media thickness was defined as the distance between the leading edge of the lumen-intima interface of the far wall to the leading edge of the media-adventitia interface of the far wall. The lumen diameter was defined as the distance between the leading edges
10 of the intima-lumen interface of the near wall and the lumen-intima interface of the far wall.

The three values in each box are the baseline value, the result after three-year follow-up and the difference therebetween given as mean $\pm$ standard deviation (SD).

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TABLE II

Characteristics	Combination therapy (n = 35)	Placebo (n = 44)	p-value for difference between groups during follow-up
IMT _{mean} common carotid (mm)	0.905 $\pm$ 0.232 0.867 $\pm$ 0.171 - 0.038 $\pm$ 0.187	0.892 $\pm$ 0.177 0.922 $\pm$ 0.188 0.030 $\pm$ 0.103	p < 0.05
IMT _{mean} carotid bulb (mm)	1.342 $\pm$ 0.410 1.392 $\pm$ 0.428 0.050 $\pm$ 0.353	1.249 $\pm$ 0.407 1.272 $\pm$ 0.348 0.023 $\pm$ 0.275	n.s.
LD _{mean} (mm)	6.296 $\pm$ 0.780 6.154 $\pm$ 0.851 - 0.142 $\pm$ 0.381	6.234 $\pm$ 0.707 6.135 $\pm$ 0.689 - 0.099 $\pm$ 0.269	n.s.

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As is evident from Table II, the patients of the combination group reduced the intima-thickness on average from 0.905 mm to 0.869 mm (n.s.), while the placebo group increased the intima-media thickness on average from 0.892 mm to 0.922 mm (n.s.).

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CLAIMS

1. A pharmaceutical combination, comprising a betablocker and a cholesterol-lowering agent.
2. The pharmaceutical combination according to claim 1, wherein the betablocker is selected from the group consisting of acebutolol, alprenolol, amosulalol, arotinolol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucumolol, bufetolol, bufuralol, bunitrolol, buprandolol, butofilolol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, cloranolol, dilevalol, epanolol, indenolol, labetalol, levobunolol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivalol, nipradilol, oxprenolol, perbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sufinalol, talindol, tertatolol, tilisolol, timolol, toliprolol, and xibenolol, and pharmaceutically acceptable salts or solvates thereof, or solvates of such salts.
3. The pharmaceutical combination according to claim 2, wherein the betablocker is metoprolol or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.
4. The pharmaceutical combination according to claim 3, wherein the betablocker is metoprolol succinate or metoprolol tartrate.
5. The pharmaceutical combination according to any previous claim, wherein the cholesterol-lowering agent is an HMG-CoA reductase inhibitor.
6. The pharmaceutical combination according to claim 5, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of atorvastatin, cerivastatin, lovastatin, nivastatin, pravastatin and simvastatin.
7. The pharmaceutical combination according to claim 5, wherein the HMG-CoA reductase inhibitor is fluvastatin.

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8. The pharmaceutical combination according to claim 5, wherein the HMG-CoA reductase inhibitor is of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-{methyl(methylsulfonyl)-amino}-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

9. The pharmaceutical combination according to any previous claim, wherein the molar ratio between the betablocker and the cholesterol-lowering agent lies in the range of from about 1000:1 to about 1:1000, particularly from 300:1 to 1:300.

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10. A pharmaceutical formulation, comprising a betablocker and a cholesterol-lowering agent in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

11. The pharmaceutical formulation according to claim 10, wherein the betablocker is selected from the group consisting of acebutolol, alprenolol, amosulalol, arotinolol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucumolol, bufetolol, bufuralol, bunitrolol, buprandolol, butofilolol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, cloranolol, dilevalol, epanolol, indenolol, labetalol, levobunolol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivalol, nipradilol, oxprenolol, perbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sufinalol, talindol, tertatolol, tilisolol, timolol, toliprolol, and xibenolol, and pharmaceutically acceptable salts or solvates thereof, or solvates of such salts.

12. The pharmaceutical formulation according to claim 11, wherein the betablocker is metoprolol or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

13. The pharmaceutical formulation according to claim 12, wherein the betablocker is metoprolol succinate or metoprolol tartrate.

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14. The pharmaceutical formulation according to any one of claims 10-13, wherein the cholesterol-lowering agent is an HMG-CoA reductase inhibitor.

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15. The pharmaceutical formulation according to claim 14, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of atorvastatin, cerivastatin, lovastatin, nivistatin, pravastatin and simvastatin.

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16. The pharmaceutical formulation according to claim 14, wherein the HMG-CoA reductase inhibitor is fluvastatin.

17. The pharmaceutical formulation according to claim 14, wherein the HMG-CoA
10 reductase inhibitor is of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

18. The pharmaceutical formulation according to any one of claims 10 to 17, wherein the
15 molar ratio between the betablocker and the cholesterol-lowering agent lies in the range of from about 1000:1 to about 1:1000, particularly from 300:1 to 1:300.

19. A kit of parts comprising:

- (i) a vessel containing a betablocker and
20 (ii) a vessel containing a cholesterol-lowering agent,
and instructions for the sequential, separate or simultaneous administration of the betablocker and cholesterol-lowering agent to a patient in need thereof.

20. The kit of parts according to claim 19, wherein the betablocker is metoprolol or a
25 pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

21. The kit of parts according to claims 19 or 20, wherein the betablocker is metoprolol succinate or metoprolol tartrate.

22. The kit of parts according to any one of claims 19 to 21, wherein the cholesterol-lowering agent is an HMG-CoA reductase inhibitor.

23. The kit of parts according to claim 22, wherein wherein the HMG-CoA reductase inhibitor is selected from the group consisting of atorvastatin, cerivastatin, lovastatin, nivistatin, pravastatin and simvastatin.

24. The kit of parts according to claim 22, wherein the HMG-CoA reductase inhibitor is fluvastatin.

25. The kit of parts according to claim 22, wherein the HMG-CoA reductase inhibitor is of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

26. The kit of parts according to any one of claims 19 to 25, wherein the molar ratio between the betablocker and the cholesterol-lowering agent lies in the range of from about 1000:1 to about 1:1000, particularly from 300:1 to 1:300.

27. A kit of parts comprising:

- (i) a pharmaceutical formulation containing a betablocker in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; and
 - (ii) a pharmaceutical formulation containing a cholesterol-lowering agent, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier;
- which betablocker and cholesterol-lowering agent are each provided in a form that is suitable for administration in conjunction with the other.

28. The kit of parts according to claim 27, comprising the betablocker and cholesterol-lowering agent as a combined preparation for simultaneous, separate or sequential use in atherosclerosis therapy.

29. The kit of parts according to claim 27 or 28, wherein the betablocker is metoprolol or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

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30. The kit of parts according to any one of claims 27 to 29, wherein the betablocker is metoprolol succinate or metoprolol tartrate.

31. The kit of parts according to any one of claims 27 to 30, wherein the cholesterol-lowering agent is an HMG-CoA reductase inhibitor.

32. The kit of parts according to claim 31, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of atorvastatin, cerivastatin, lovastatin, nivistatin, pravastatin and simvastatin.

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33. The kit of parts according to claim 31, wherein the HMG-CoA reductase inhibitor is fluvastatin.

34. The kit of parts according to claim 31, wherein the HMG-CoA reductase inhibitor is of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

35. The kit of parts according to any one of claims 27 to 34, wherein the molar ratio between the betablocker and the cholesterol-lowering agent lies in the range of from about 1000:1 to about 1:1000, particularly from 300:1 to 1:300.

36. A combination according to any one of claims 1 to 9, a formulation according to any one of claims 10 to 18, or a kit of parts according to any one of claims 19 to 35, for use in medical therapy.

37. A method for prophylactic or therapeutic treatment of a patient suffering from, or susceptible to, atherosclerosis which method comprises administering to the patient a therapeutically effective total amount of

(i) a betablocker in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; in conjunction with

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(ii) a cholesterol-lowering agent in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

38. The method according to claim 37, wherein the administration of the betablocker and the cholesterol-lowering agent is simultaneous, separate or sequential.

39. The method according to any one of claims 37 to 38, wherein the betablocker is metoprolol or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

40. The method according to claim 39, wherein the betablocker is metoprolol succinate or metoprolol tartrate.

41. The method according to any one of claims 37 to 40, wherein the cholesterol-lowering agent is an HMG-CoA reductase inhibitor.

42. The method according to claim 41, wherein the HMG-CoA reductase inhibitor is fluvastatin.

43. The method according to claim 42, wherein the HMG-CoA reductase inhibitor is (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]-pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

44. The method according to any one of claims 37 to 43, wherein the molar ratio between the betablocker and the cholesterol-lowering agent lies in the range of from about 1000:1 to about 1:1000, particularly from 300:1 to 1:300.

45. A method for prophylactic or therapeutic treatment of a patient suffering from, or susceptible to, atherosclerosis which method comprises administering to the patient a formulation as defined in any one of claims 10 to 18.

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46. A method according to claim 45, wherein the patient suffers from, or is susceptible to, hypercholesterolemia or hyperlipoproteinemia.

47. The use of a formulation according to any one of claims 10 to 18, in the manufacture of a medicament for the prophylactic or therapeutic treatment of atherosclerosis.

48. The use according to claim 47, wherein the patient suffers from or, is susceptible to, hypercholesterolemia or hyperlipoproteinemia.

49. The use according to claim 47 or 48, wherein the betablocker is metoprolol or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

50. The use according to claim 49, wherein the betablocker is metoprolol succinate or metoprolol tartrate.

51. The use according to any one of claims 47 to 50, wherein the cholesterol-lowering agent is an HMG-CoA reductase inhibitor.

52. The use according to claim 51 wherein the HMG-CoA reductase inhibitor is fluvastatin.

53. The use according to claim 50, wherein the HMG-CoA reductase inhibitor is (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

54. The use according to any one of claims 47 to 53 wherein the molar ratio between the betablocker and the cholesterol-lowering agent lies in the range of from about 1000:1 to about 1:1000, particularly from 300:1 to 1:300.

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N**ABSTRACT**

The present invention relates to pharmaceutical formulations a betablocker and a
cholesterol-lowering agent in admixture with a pharmaceutically acceptable adjuvant,
diluent or carrier, as well as a kit of parts, a method for treatment and use of the
formulations for the prophylactic or therapeutic treatment of atherosclerosis, hyper-
cholesterolemia and hyperlipoproteinemia.

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REQUISITOS NEC

AGILIZACIÓN DEL TRÁMITE

USUARIO RADICADOR

PATENTE DE INVENCIÓN [X]

MODELO DE UTILIDAD

[] [X]

- Indicación de que se solicita la concesión de una patente [] [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [] [X]
- Descripción de la invención [] [X]
- Dibujos de ser estos pertinentes [] [X]
- Comprobante de Pago de las tasas establecidas [] [X]

COMPLETA [X]

INCOMPLETA

[] []

DISEÑO INDUSTRIAL []

- Indicación de que se solicita el registro de Diseño Industrial [] []
- Datos de identificación del solicitante o de la persona que presenta la solicitud [] []
- Representación gráfica y/o gráfica del Diseño Industrial o muestra del material que incorpora el diseño [] []
- Comprobante de pago de las tasas establecidas [] []

COMPLETA []

INCOMPLETA

[] []

ESQUEMA DE TRAZADO []

- Indicación de que se solicita el registro de un Esquema de trazado [] []
- Datos de identificación del solicitante o de la persona que presenta la solicitud [] []
- Representación gráfica del esquema de trazado [] []
- Comprobante de pago de las tasas establecidas [] []

COMPLETA []

INCOMPLETA

[] []

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Fecha: _____

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2020
Bogotá, D.C.,

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Apoderado
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Oficio N° 07218

ASUNTO:	Radicación N°	02-89167
	Solicitud Internacional	PCT/SE01/00663
	Fecha inicio fase nacional	03/11/2002
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- ☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 28-k) Decisión 486).
- ☐ La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsecuentes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredite la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 05 SET. 2003.