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Delegatura de Propiedad Industrial

Division de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCION

PCT

02-89167

21 EXPEDIENTE No

54 TÍTULO Nueva Combinación de un Bet-Bloqueador
y un Agente que Reduce el colesterol

51 CLASIFICACIÓN INTERNACIONAL A61K 45/06

71 SOLICITANTE Astroczeneca AB

DOMICILIO Sodertalje, Suecia

74 APODERADO Ramiro Castro Duque

22 BOGOTÁ, D C ,

202038

(FORMA P 10)

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PETITORIO

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:			
☒ Patente de Invención.		☐ Patente de Modelo de Utilidad.	
☐ Capítulo I.		☒ Capítulo II.	
2 SOLICITANTE (71)	Nombre: ASTRAZENECA AB Dirección: S-151 85 Sodertalje, Suecia Nacionalidad o Domicilio: Suecia Lugar de Constitución: Suecia Teléfono: Fax: E-mail		IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: RAMIRO CASTRO DUQUE Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:		IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>170.322 TP_1003</u>
4 INVENTOR (ES) (72)	Nombre: Göran Bondjers, Olov Wiklund, John Wikstrand Dirección: Lagman Lumbers Väg 8, S-443 34 Lerum, SE; Ljungmarksgatan 9, S-431 69 Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE Nacionalidad o Domicilio: Suecia		
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9 Título (54): <u>NUEVA COMBINACIÓN DE UN BETA - BLOQUEADOR Y UN AGENTE QUE REDUCE EL COLESTEROL</u>			
7 Clasificación Internacional (51) <u>A61K 45/06</u>			
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Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.			

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ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$378.000
- ☒ Comprobante de pago por reivindicación de prioridad. \$212.000
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☐ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ Otros

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente.

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA: _____

C.C. 170.322 de Bogotá T.P. 1003 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

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FECHA : AGOSTO 23 DE 2002

CONSIGNACION

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PAGO	Vr PAGO
RANIRO CASTRO	CONSIGNACION	BANCO POPULAR	050-00110-6	5733220	23/08/2002	1,074,000 00

CONCEPTO

CANT	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005 01-01	SOLICITUDES	
		02 INVOCACION DE UNA PRIORIDAD EN LA	106 000 00
		TOTAL :	106,000 00

SON: CIENTO SEIS MIL PESOS

RESPONSABLE

RECIBO DE CAJA APLICADO AL EXPEDIENTE No _____

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NIT : 800174089-2

SUPERINDUSTRIA Y COMERCIO

Radicacion : 02089167 00000000Folios 29

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Dependencia 2020 DIVISION DE NUEVAS CREACIONES

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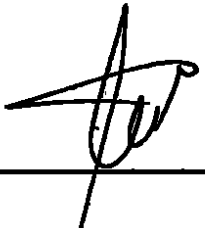
CONSIGNACION

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PGO	Vr PAGO
RANIRO CASTRO	CONSIGNACION	BANCO POPULAR	090-00110-6	5733220	23/08/2002	1,074,000 00

CONCEPTO

CANT	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	02 INVOCACION DE UNA PRIORIDAD EN MU	106,000 00
		TOTAL	106 000 00

SON: CIENTO SEIS MIL PEROS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No _____

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Industria y Comercio

SUPERINTENDENCIA

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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº PAGO	FECHA PGO	Vr PAGO
RAIRO CASTRO	CONSIGNACION	BANCO POPULAR	050-00110-6	5733220	23/08/2002	1,074,000 00

***** CONCEPTO *****

CANT	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	
	1 TRAMITES DE SOL. DE PATENTE DE IN	378 000 00
	TOTAL :	378,000 00

SON: TRESCIENTOS SETENTA Y OCHO MIL PESOS

RESPONSABLE : 

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WO 01/74394 A1

(54) Title: NEW COMBINATION OF A BETABLOCKER AND A CHOLESTEROL-LOWERING AGENT

(57) Abstract: The present invention relates to pharmaceutical formulations comprising 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, hypercholesterolemia and hyperlipoproteinemia.

NEW COMBINATION OF A BETABLOCKER AND A CHOLESTEROL-LOWERING AGENT

FIELD OF THE INVENTION

5 The present invention relates to pharmaceutical formulations comprising 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 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 large e.g. patients suffering from hypercholesterolemia and hyperlipoproteinemia.

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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 density lipid (LDL) cholesterol.

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Betablockers on the other hand are known to have a positive influence on various cardiovascular disease primarily hypertension whereas physicians have generally avoided prescription of betablockers for patients with hypercholesterolemia.

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

30

The administration of combinations of β_1 selective blockers and lipid lowering drugs to healthy volunteers in order to observe the effects on fat metabolism ammonia levels and the perception of effort during exercise was disclosed in Br J Clin Pharmacol 1997 vol 43 no 3 pages 291-300 The combinations studied were 1) metoprolol (controlled release) and fluvastatin 2) metoprolol (controlled release) and bezafibrate 3) atenolol (normal release) and fluvastatin and 4) atenolol (normal release) and bezafibrate The paper concluded that that these four combinations each caused significant reductions in fat metabolism increased plasma ammonia concentrations and raised the perception of exercise Combination 1) had the least adverse effect but the formulation difference was thought to be a significant factor in explaining the differences observed with respect to combination 3)

The effects of a combination of pravastatin and atenolol on hypertensive and hypercholesterolaemic patients was reported in Scand J Prim Health Care 1999 vol 17 122 127 The conclusion was that the effect of atenolol was not influenced by the concurrent administration of pravastatin and vice versa However lifestyle intervention was also a feature of this study and therefore the conclusions which can be drawn from this study are not clear

A *post hoc* analysis of patients who had been treated with lovastatin and who were also receiving antihypertensive medication including β_1 adrenergic receptor blockers was reported in Hypertension 1992 Vol 19 3 242 The paper concluded that subject to a number of limitations there was no evidence for an attenuation of the lovastatin induced changes in lipids and lipoproteins or an alteration in the safety profile of lovastatin when administered concurrently with commonly used antihypertensive agents

It was concluded in Presse Med Volume 1996 vol 25 no 40 2013-2016 that the effect of the β_1 adrenergic receptor blocker atenolol was not diminished in combination with pravastatin However the effect of pravastatin on lipid metabolism was more favourable

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when pravastatin was combined with the angiotensin converting enzyme inhibitor captopril rather than with atenolol

WO98/02357 discloses a carton for carrying pharmaceutically active substances or combinations thereof. One such combination mentioned is the combination of a beta blocker such as metoprolol or isosorbide mononitrate and a lipid lowering substance such as fluvastatin. This application does not disclose any data concerning the effects of such a combination.

WO 99/11260 discloses a combination of atorvastatin and an antihypertensive agent. No data are disclosed in this application.

WO97/38694 discloses a combination of an HMG CoA reductase (3 hydroxy-3 methylglutaryl coenzyme A reductase) inhibitor in combination with folic acid in combination with a drug selected from a range of other types of drug including beta blockers.

WO 00/38725 discloses combinations of an ileal bile transport inhibitor and a range of other types of drug including antihypertensive drugs for example beta blockers. No data are presented.

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 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.

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 for which such administration is necessary or advantageous

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

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DETAILED DESCRIPTION OF THE INVENTION

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

15

In one aspect the present invention thus relates to pharmaceutical combinations comprising a betablocker and a HMG-CoA reductase inhibitor wherein the betablocker is selected from the group consisting of acebutolol alprenolol amosulalol aroundolol
 20 atenolol befunolol betaxolol bevantolol bisoprolol bopindolol bucumolol bufetolol
 bufuralol bunitrolol buprandolol butofilolol carazolol carteolol carvedilol celiprolol
 cetamolol cioranolol dilevalol epanolol indenolol labetalol levobunolol mepindolol
 metopranolol metoprolol moprolol nadolol nadoxolol nebivalol nipradilol oxprenolol
 perbutolol pindolol practolol pronethalol propranolol sotalol sufinalol talindol
 25 tertatolol tilisolol umolol toliprolol and xibenolol and pharmaceutically acceptable salts
 or solvates thereof or solvates of such salts and the HMG CoA reductase inhibitor is
 selected from the group consisting of cerivastatin itavastatin lovastatin mevastatin
 nicostatin nivastatin and (E) 7 [4-(4 fluorophenyl)-6-isopropyl-2-
 [methyl(methylsulfonyl)amino]-pyrimidin 5 yl](3R 5S) 3,5-dihydroxyhept-6-enoic acid or
 30 a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt.
 comprising a betablocker and a cholesterol lowering agent

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

- 5 A further aspect of the present invention relates to kits of parts comprising
- (i) a vessel containing a betablocker and
 - (ii) a vessel containing a HMG CoA reductase inhibitor which 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, especially sodium or
- 10 calcium or solvate thereof or a solvate of such a salt
- and instructions for the sequential, separate or simultaneous administration of the betablocker and a HMG CoA reductase inhibitor to a patient for which such administration is necessary or advantageous.
- 15 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 with a pharmaceutically acceptable adjuvant, diluent or carrier.
- 20 wherein the betablocker and the 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 comprising a betablocker and a cholesterol-lowering agent are administered,

25 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 treatment of the relevant condition than if either of the two formulations are administered

30 (optionally repeatedly) alone in the absence of the other formulation over the same course of treatment. It must, however, be emphasized that betablockers have never been used previously to give an anti-atherosclerotic effect e.g. in patients suffering from hyper

cholesterolemia or hyperlipoproteinemia. 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 skilled in the art

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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 "administered simultaneously" and "administered at the same time as" include that individual
10 doses of a betablocker and a cholesterol lowering agent are administered within 48 hours e.g. 24 hours of each other

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
15 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
(ii) a cholesterol lowering agent in admixture with a pharmaceutically acceptable adjuvant diluent or carrier

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

In a further aspect of the invention relates to methods for prophylactic or therapeutic treatment of a patient suffering from or susceptible to atherosclerosis which method
30 comprises administering to the patient a pharmaceutical combination consisting essentially of
(i) a betablocker and

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(ii) a cholesterol-lowering agent

In 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 combination consisting of

(i) a betablocker and

(ii) a cholesterol lowering agent

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

(i) a betablocker and

(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

Betablockers

In the present application the term betablockers refers to any pharmaceutical agent that as part of its pharmacological action blocks beta one receptors

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, bufetolol, bufuralol, bunitrolol, buprandolol, butofilolol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, cloranolol, dilevalol, epanolol, indenolol, labetalol, levobunolol, mepindolol, metopranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivalol, nipradilol, oxprenolol, perbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sufinalol, talindol, tertatolol, ulisolol, timolol, toliprolol and xibenolol and pharmaceutically acceptable salts or solvates thereof or solvates of such salts

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) metoprolol tartrate or metoprolol fumarate.

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The pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers of a betablocker are within the scope of the present invention. It should also be understood that all the diastereomeric forms possible are within the scope of the invention.

- 10 In the present application the term "betablocker" also includes chemical modifications of the betablockers such as esters, prodrugs and metabolites, whether active or inactive.

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, fluvastatin, itavastatin, lovastatin, mevastatin, nicotianic acid, niva-
 20 statin, pravastatin and simvastatin or a pharmaceutically acceptable salt, especially sodium or calcium, or a solvate thereof or a solvate of such a salt. A particularly preferred statin is however a compound with the chemical name (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid [also known as (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[N-methyl-N-(methylsulfonyl)-amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] or a pharmaceutically
 25 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. This latter statin is now known under its generic name
 30 rosuvastatin.

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In the present application the term cholesterol lowering agent also includes chemical modifications of the HMG-CoA reductase inhibitors such as esters prodrugs and metabolites whether active or inactive

5 Pharmaceutical formulations

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

10 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 compound with the chemical name (E) 7 [4-(4-fluorophenyl)-6 isopropyl 2 [methyl(methylsulfonyl)-amino] pyrimidin-5 yl](3R,5S) 3 5-dihydroxyhept 6-enoic acid
15 or a pharmaceutically acceptable salt especially the calcium and sodium salts, or solvate thereof or a solvate of such a salt

A most preferred combination comprises metoprolol particularly metoprolol succinate or metoprolol tartrate and (E)-7 [4-(4 fluorophenyl) 6-isopropyl 2 [methyl(methylsulfonyl)
20 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

In the present invention the formulation and/or kits of parts may comprise two or more
25 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 pharmaceutical formulation for oral intravenous subcutaneous tracheal bronchial
30 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

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)

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 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

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.

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

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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
10 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

Solutions for parenteral administration may be prepared as a solution of a formulation of
15 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

20 The dose of the compounds 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.

The typical daily dose of the active ingredients varies within a wide range and will depend
25 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 1000 mg per day of total active ingredients.

30 For the cholesterol lowering agent, any dose used in clinical practice may be used in the formulations and kits of parts of the present invention.

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.

5

Medical and pharmaceutical use

Also provided according to the present invention are formulations and kits of parts for use in medical therapy and particularly for use in the prophylactic or therapeutic treatment of atherosclerosis the use of formulations of the present invention in the manufacture of medicaments for use in the prophylactic or therapeutic treatment of atherosclerosis and methods of medical treatment or prophylaxis comprising the administration of a therapeutically effective total amount of a betablocker and a cholesterol lowering agent to a patient suffering from, or susceptible to atherosclerosis

15

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.

20

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.

More particularly the formulations of the invention are expected to be useful in prevention of clinical events associated with the progression of atherosclerosis and/or acute vascular accidents related to atherosclerotic disease and plaque including but not limited to stroke myocardial infarction (MI) congestive heart failure (CHF) cognitive decline peripheral vascular disease and renal dysfunction

30

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 hypertension diabetes mellitus congestive heart failure (CHF) myocardial infarction
5 (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

10 **EXAMPLE**

A three year placebo-controlled pilot study was designed to investigate the effect of the betablocker metoprolol on ultrasound assessed atherosclerosis in patients with primary hypercholesterolemia on concomitant therapy with a cholesterol lowering agent. More particularly the trial was a prospective randomised double blind study the betablocker
15 was a controlled release formulation of metoprolol succinate (metoprolol CR/XL) and the effect was assessed by measuring the intima media thickness (IMT) in the carotid artery of the patients

Intima media thickness of the common carotid artery is commonly used as a surrogate
20 variable for generalized atherosclerosis including coronary atherosclerosis (Wikstrand J Wiklund O. Frontiers in cardiovascular science. Quantitative measurements of atherosclerotic manifestations in humans. Arterioscl Thromb 1992; 12: 114-119 and Grobbee DE, Bots ML. Carotid artery intima media thickness as an indicator of generalized atherosclerosis. J Int Med. 1994; 236: 567-573). Accordingly IMT of the
25 common carotid artery was selected as the major endpoint of the study. Good quality images of the far wall of the straight part of the common carotid artery are easy to obtain and IMT can be measured in nearly all subjects with good reproducibility (Schmidt C, Wendelhag I. How can the variability in ultrasound measurement of intima media thickness be reduced? Studies of interobserver variability in carotid and femoral arteries
30 Clin Phys 1999; 19: 45-55).

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

5 Patients with hypercholesterolemia (n=129) were randomized at placebo-run in 62 to metoprolol CR/XL (AstraZeneca, Mölndal, Sweden) treatment (100 mg o.d.) and 67 to placebo. During the two-weeks of placebo run, 15 subjects from the metoprolol CR/XL group and 11 subjects from the placebo group were withdrawn due to negative ultrasound examinations (n=3 and n=1 respectively), low total cholesterol, low LDL cholesterol or
 10 high triglyceride levels (n=6 and n=4 respectively), myocardial infarction (n=1 and n=0 respectively), nausea (n=1 and n=2 respectively), unwillingness to participate (n=4 and n=2 respectively) and other causes (n=0 and n=2 respectively).

After start of double blind treatment, 12 subjects from the metoprolol CR/XL group and 12
 15 subjects from the placebo group were withdrawn due to myocardial infarction (n=2 and n=1 respectively), atrial fibrillation (n=2 and n=0 respectively), angina pectoris (n=1 and n=1 respectively), malignancy (n=1 and n=1 respectively), minor side effects (n=1 and n=5 respectively), given metoprolol CR/XL by other physician (n=0 and n=1 respectively), moved to other area (n=2 and n=0), compliance (n=1 and n=1 respectively)
 20 and unwillingness (n=2 and n=2 respectively).

Subsequently, seventy-nine patients completed the study: 35 in the metoprolol CR/XL group and 44 in the placebo-group. The distribution of males and females in the groups were similar: 18 and 22 males and 17 and 22 females in the metoprolol CR/XL and
 25 placebo group respectively. Likewise, the mean age was 60.6 and 59.6 for the metoprolol CR/XL and placebo group respectively. The mean follow-up time was 2.97 years.

All analyses for the patients with hypercholesterolemia in the present example refers to the 79 subjects who completed the study. Two subjects in each group reduced the dose during
 30 follow-up from 100 mg to 50 mg (metoprolol CR/XL or placebo).

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cholesterol HDL cholesterol and heart rate decreased more in the metoprolol CR/XL group compared with the placebo group ($p < 0.05$)

lipid lowering therapy in the metoprolol CR/XL group and the placebo group follow up

Patients were treated with statins before inclusion 31% in the metoprolol CR/XL group and 15% in the placebo group. However, all lipid lowering drugs were withdrawn prior to the double blind medication.

A majority of subjects in the metoprolol CR/XL group and in the placebo group were treated with statins at the 1 year follow up (91% and 80% respectively), at the 2 year follow up (88% and 82% respectively), and at the 3-year follow up (94% and 84% respectively). Ninety four percent of the subjects in the metoprolol CR/XL group and 89% of subjects in the placebo group were at any time during the 3 year follow up treated with statins. Subjects were also treated with cholestyramine at the 1 year follow-up (23% in the metoprolol CR/XL group and 20% respectively), at the 2 year follow up (26% and 23% respectively), and at the 3 year follow up (26% and 23% respectively). All in the metoprolol CR/XL group and 96% of subjects in the placebo group were treated with any lipid lowering drug during the follow up.

At the 3 year follow up LDL cholesterol was reduced by 44% in the metoprolol CR/XL group and by 38% in the placebo group (non-significant difference between groups).

Carotid intima media thickness (IMT) and lumen diameter in the three groups during follow up

Carotid intima media thickness was defined as the distance between the leading edge of the intima-media 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

of the intima lumen interface of the near wall and the lumen intima interface of the far wall

Mean values for common carotid IMT at the base line examination and at the 3-year follow up were 0.91 ± 0.23 and 0.87 ± 0.17 mm respectively in the metoprolol CR/XL group and 0.89 ± 0.18 and 0.92 ± 0.17 mm respectively in the placebo group ($p < 0.05$ between groups for difference in change during follow up) The regression coefficient for the yearly change in common carotid IMT was -0.010 ± 0.06 mm and $+0.012 \pm 0.04$ for the metoprolol CR/XL group and the placebo group respectively and the 95% CI for the difference between the placebo group and the metoprolol CR/XL group was 0.0004 to 0.0444 mm ($p < 0.05$)

Mean values for carotid bulb IMT at the base line examination and at the 3-year follow up were 1.42 ± 0.46 and 1.34 ± 0.41 mm respectively in the metoprolol CR/XL group and 1.26 ± 0.45 and 1.30 ± 0.41 mm respectively in the placebo group ($p = 0.12$ between groups for difference in change during follow-up)

Mean values for lumen diameter in the carotid artery at the base-line examination and at the 3 year follow up were 6.30 ± 0.78 and 6.15 ± 0.85 mm respectively in the metoprolol CR/XL group and 6.23 ± 0.71 and 6.14 ± 0.69 mm, respectively in the placebo group (no significant differences between groups)

Mean values for baseline common carotid IMT in subjects that were withdrawn from double-blind medication during follow up were 0.86 ± 0.11 and 0.89 ± 0.17 mm in the metoprolol CR/XL group and the placebo group respectively (no significant difference between groups)

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CLAIMS

- 1 A pharmaceutical combination comprising a betablocker and a HMG-CoA reductase
5 inhibitor 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 metopranolol metoprolol moprolol nadolol
10 nadoxolol nebivalol nipradilol oxprenolol perbutolol pindolol practolol pronethalol
propranolol sotalol sufinalol talinolol tertatolol ulisolol timolol toliprolol and
xibenolol and pharmaceutically acceptable salts or solvates thereof or solvates of such
salts and the HMG-CoA reductase inhibitor is selected from the group consisting of
cerivastatin itavastatin lovastatin mevastatin nicostatin nivastatin and (E) 7-[4-(4-
15 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.
- 2 The pharmaceutical combination according to claim 1 wherein the betablocker is
20 metoprolol or a pharmaceutically acceptable salt or solvate thereof or a solvate of such a
salt.
- 3 The pharmaceutical combination according to claim 2 wherein the betablocker is
metoprolol succinate metoprolol tartrate or metoprolol fumarate
25
- 4 The pharmaceutical combination according to any previous claim 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 especially sodium or calcium or solvate thereof or a
30 solvate of such a salt.

- 5 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
- 6 A pharmaceutical formulation comprising a betablocker and a cholesterol lowering agent in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier
- 7 A pharmaceutical formulation according to claim 6 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, ulisolol, umolol, toliprolol, and xibenolol, and pharmaceutically acceptable salts or solvates thereof or solvates of such salts
- 8 The pharmaceutical formulation according to claim 7 wherein the betablocker is metoprolol or a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt
- 9 The pharmaceutical formulation according to claim 8 wherein the betablocker is metoprolol succinate, metoprolol tartrate or metoprolol fumarate
- 10 The pharmaceutical formulation according to any one of claims 6 to 9 wherein the cholesterol-lowering agent is an HMG-CoA reductase inhibitor
- 11 The pharmaceutical formulation according to claim 10 wherein the HMG CoA reductase inhibitor is selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, itavastatin, lovastatin, mevastatin, nicostatin, nivistatin, pravastatin and simvastatin or a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt

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12 The pharmaceutical formulation according to claim 11 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 especially sodium or calcium or solvate thereof or a solvate of such a salt

5

13 The pharmaceutical formulation according to any one of claims 6 to 12 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

10 14 A kit of parts comprising

(i) a vessel containing a betablocker and

(ii) a vessel containing a HMG CoA reductase inhibitor which 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 especially sodium or

15 calcium or solvate thereof or a solvate of such a salt

and instructions for the sequential, separate or simultaneous administration of the betablocker and a HMG CoA reductase inhibitor to a patient for which such administration is necessary or advantageous

20 15 The kit of parts according to claim 14 wherein the betablocker is metoprolol or a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt

16 The kit of parts according to claims 14 or 15 wherein the betablocker is metoprolol succinate, metoprolol tartrate or metoprolol fumarate

25

17 The kit of parts according to any one of claims 14 to 16 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

30 18 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 wherein the betablocker and the cholesterol lowering agent are each provided in a form that is suitable for administration in conjunction with the other
- 5
- 19 The kit of parts according to claim 18 comprising the betablocker and the cholesterol lowering agent as a combined preparation for simultaneous separate or sequential use in atherosclerosis therapy
- 10
- 20 The kit of parts according to claim 18 or 19 wherein the betablocker is metoprolol or a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt
- 21 The kit of parts according to any one of claims 18 to 20 wherein the betablocker is metoprolol succinate metoprolol tartrate or metoprolol fumarate
- 15
- 22 The kit of parts according to any one of claims 18 to 21 wherein the cholesterol-lowering agent is an HMG CoA reductase inhibitor
- 23 The kit of parts according to claim 22 wherein the HMG-CoA reductase inhibitor is
- 20
- selected from the group consisting of atorvastatin cerivastatin fluvastatin itavastatin lovastatin mevastatin nicostatin ruvastatin pravastatin and simvastatin or a pharmaceutically acceptable salt or a solvate thereof or a solvate of such a salt
- 24 The kit of parts according to claim 23 wherein the HMG-CoA reductase inhibitor is of
- 25
- (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 sodium or calcium or solvate thereof or a solvate of such a salt
- 25
- 25 The kit of parts according to any one of claims 18 to 24 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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26 A combination according to any one of claims 1 to 5 a formulation according to any one of claims 6 to 13 or a kit of parts according to any one of claims 14 to 25 for use in medical therapy

5 27 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

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

28 The method according to claim 27 wherein the administration of the betablocker and the cholesterol lowering agent is simultaneous separate or sequential

15

29 The method according to any one of claims 27 to 28 wherein the betablocker is metoprolol or a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt

20 30 The method according to claim 29 wherein the betablocker is metoprolol succinate metoprolol tartrate or metoprolol fumarate

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

25

32 The method according to claim 31 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 especially sodium or calcium or solvate thereof or a solvate of such a salt

30

33 The method according to any one of claims 27 to 32 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

5 34 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 6 to 13

35 A method according to claim 34 wherein the patient suffers from or is susceptible to
10 hypercholesterolemia or hyperlipoproteinemia

36 The use of a formulation according to any one of claims 6 to 13 in the manufacture of a medicament for the prophylactic or therapeutic treatment of atherosclerosis

15 37 The use according to claim 36 wherein the patient suffers from or is susceptible to hypercholesterolemia or hyperlipoproteinemia

38 The use according to claim 36 or 37 wherein the betablocker is metoprolol or a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt

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39 The use according to claim 38 wherein the betablocker is metoprolol succinate, metoprolol tartrate or metoprolol fumarate

40 The use according to any one of claims 36 to 39 wherein the cholesterol-lowering
25 agent is an HMG-CoA reductase inhibitor

41 The use according to claim 40 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, especially sodium or
30 calcium or solvate thereof or a solvate of such a salt

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42 The use according to any one of claims 36 to 41 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

- 5 43 The use of a combination according to any one of claims 1 to 5 a formulation according to any one of claims 6 to 13 or a kit of parts according to any one of claims 14 to 25 for use in the manufacture of a medicament for the prophylactic or therapeutic treatment of a patient suffering from or susceptible to atherosclerosis

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/00663

A CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 45/06, A61K 31/195, A61K 31/40 A61K 31/505, A61P 3/06, A61P 9/10
According to International Patent Classification (IPC) or to both national classification and IPC

B FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE DK FI NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable search terms used)

EPO INTERNAL, WPI DATA, PAJ, CHEM ABS DATA

C DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate of the relevant passages	Relevant to claim No.
P X	Atherosclerosis Volume 151 No 1 June 2000 G Berglund et al "(MoW3 3) Low dose metoprolol and fluvastatin slow progression of atherosclerosis Main results from BCAPS" page 1 - page 354 page 4 --	1-43
P X	Atherosclerosis, Volume 151 No 1 June 2000 B Hedblad J et al, "(MoP7 W3) Low dose metoprolol and fluvastatin in silent atherosclerotic disease Metabolic and adverse effects in BCAPS" page 1 - page 354 page 24 --	1-43

☒ I further documents are listed in the continuation of Box C.☒ See patent family annex.

Special categories of cited documents: A document defining the general state of the art which is not considered to be of particular relevance I earlier application or patent but published on or after the international filing date I document which may throw doubts on prior claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) O documents 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	T later document published after the international filing date or prior 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 conceived novel or cannot be considered to involve an inventive step when the document is taken alone Y document of particular relevance: the claimed invention cannot be conceived to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art & concurrent member of the same patent family
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Date of the actual completion of the international search

Date of mailing of the international search report

14 June 2001

19-06-2001

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/00663

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication where appropriate of the relevant passages	Relevant to claim No.
P X	WO 0038725 A1 (G D SEARLE & CO) 6 July 2000 (06 07 00), page 2 line 16 - line 30 page 63, line 1 - line 18 page 64, N-15-N-18 page 68, line 1 - page 70 line 1 page 114, page 116 - page 158 --	1-43
X	Br J Clin Pharmacol Vol 43, No 3 1997, C J Eagles et al "The effects of combined treatment with beta1-selective receptor antagonists and lipid-lowering drugs on fat metabolism and measures of fatigue during moderate intensity exercise a placebo-controlled study in healthy subjects", page 291 - page 300 --	1-43
X	Scand J Prim Health Care Volume 17 1999 Olav Per Foss et al "Treatment of hypertensive and hypercholesterolaemic patients in general practice" page 122 - page 127 --	1-43
X	Hypertension Volume 19 No 3 1992 James L Pool et al "Lovastatin and Coadministered Antihypertensive/Cardiovascular Agents" page 242 - page 248 page 243 --	1-43
X	Presse Med Volume 25 No 40 December 1996 S Witchitz O et al "Effets comparés du captopril et de l'atenolol sur le métabolisme lipidique chez des patients hypertendus hypercholestérolémiques traités par pravastatine" page 2013 - page 2016 --	1-43
X	Am J Health-Syst Pharm Volume 52 August 1995 William R Garnett, "Interactions with hydroxymethylglutaryl-coenzyme A reductase inhibitors" page 1639 - page 1645 page 1642 right column --	1-43

20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/00663

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate of the relevant passages	Relevant to claim No
X	WO 9802357 A1 (ASTRA AKTIEBOLAG) 22 January 1998 (22 01 98) page 7 line 25 - line 30 --	1-43
X	WO 9911260 A1 (PFIZER INC) 11 March 1999 (11 03 99), page 7 line 22 - line 26, page 18 line 22 - page 20 line 12, the claims --	1-43
X	WO 9738694 A1 (MERCK & CO INC) 23 October 1997 (23 10 97) claims 7,14,24 29 34 -- -----	1-43

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/00663

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 ☒ Claims Nos. 27-35
because they relate to subject matter not required to be searched by this Authority namely
see next sheet*
- 2 ☒ Claims Nos. 6, 10, 14, 18, 22, 27, 31, 40 all in part
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
see next sheet**

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 searched 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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Claims 31-32 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39 1 (iv) Nevertheless, a search has been executed for these claims The search has been based on the alleged effects of the compounds/compositions

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Claims 6 10,14,18,22,27,31 and 40 are too broadly formulated to permit a meaningful search Therefore, the search has mainly been restricted to the examples and the rest of the claims See PCT Article 6

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/05/01

International application No

PCT/SE 01/00663

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	0038725	A1	06/07/00	AU	2157400 A	31/07/00
				AU	2157500 A	31/07/00
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				AU	2157700 A	31/07/00
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				AU	2157900 A	31/07/00
				AU	2348000 A	31/07/00
				AU	2348100 A	31/07/00
				AU	3103800 A	31/07/00
				WO	0038721 A	06/07/00
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				US	5971261 A	26/10/99
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				BR	9811556 A	22/08/00
				CN	1268053 T	27/09/00
				EP	1009400 A	21/06/00
				HR	980474 A	30/06/99
				NO	20000996 A	27/04/00
				PL	339091 A	04/12/00
				TR	200000563 T	00/00/00
WO	9738694	A1	23/10/97	AU	732465 B	26/04/01
				AU	2666597 A	07/11/97
				CA	2251972 A	23/10/97
				EP	0904082 A	31/03/99
				GB	9612082 D	00/00/00
				JP	2000508659 T	11/07/00
				GB	9616804 D	00/00/00

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 100029-1 WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SE01/00663	International filing date (day/month/year) 27 03 2001	Priority date (day/month/year) 03 04 2000
International Patent Classification (IPC) or national classification and IPC A61K 45/06, A61K 31/195 A61K 31/40 A61K 31/505, A61P 3/06 A61P 9/10		
Applicant AstraZeneca Aktiebolag et al		

1 This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36
2 This REPORT consists of a total of <u>7</u> sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of _____ sheets.
3 This report contains indications relating to the following items: I ☒ Basis of the report II ☐ Priority III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement VI ☒ Certain documents cited VII ☐ Certain defects in the international application VIII ☒ Certain observations on the international application

Date of submission of the demand 09 10 2001	Date of completion of this report 12 06 2002
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88	Authorized officer Gerd Strandell/EÖ Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE01/00663

23

1 Basis of the report

1 With regard to the elements of the international application:*

- ☒ the international application as originally filed
- ☐ the description.
pages _____ as originally filed
pages _____ filed with the demand
pages _____ filed with the letter of _____
- ☐ the claims.
pages _____ as originally filed
pages _____ as amended (together with any statement) under article 19
pages _____ filed with the demand
pages _____ filed with the letter of _____
- ☐ the drawings.
pages _____ as originally filed
pages _____ filed with the demand
pages _____ filed with the letter of _____
- ☐ the sequence listing part of the description.
pages _____ as originally filed
pages _____ filed with the demand
pages _____ filed with the letter of _____

2 With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is.

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3 With regard to any nucleotide and/or amino acid sequences disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing.

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4 ☐ The amendments have resulted in the cancellation of

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheet/fig. _____

5 ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (e)).**

Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as originally filed and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)

Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE01/00663

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1 The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application,

☒ claims Nos. 27-35

because

☒ the said international application, or the said claims Nos. 27-35

relate to the following subject matter which does not require an international preliminary examination (*specify*)

See PCT Rule 67 1 (iv) Methods for treatment of the human or animal body by surgery or therapy as well as diagnostic methods

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 6, 10, 14, 18 22 and 40 all in part are so unclear that no meaningful opinion could be formed (*specify*)

Claims 6, 10 14 18, 22 and 40 are too broadly formulated to permit a meaningful search. Therefore the search has mainly been restricted to the examples and the rest of the claims. See PCT, Article 6. Consequently, the opinion is based on what is searched. Confer PCT, Rule 66 1 (e)

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

2 A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions.

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V Reasoned statement under Article 35(2) with regard to novelty inventive step or industrial applicability citations and explanations supporting such statement

1 Statement

Novelty (N)	Claims	<u>3 5 9 12 17 21 24 25 39 41 42</u>	YES
	Claims	<u>1 2 6 8 10 11 18 20 22 23 26 36 38 40, 43</u>	NO
Inventive step (IS)	Claims	_____	YES
	Claims	<u>1-26, 36-43</u>	NO
Industrial applicability (IA)	Claims	<u>1-26, 36-43</u>	YES
	Claims	_____	NO

2 Citations and explanations (Rule 70.7)

The opinion on claims 1-26 and 36-43 is based on what is searched according to part III in this report Confer PCT, Rule 66 1 (e)

The following documents are cited

- D1) Br J Clin Pharmacol, Vol 43 No 3, 1997
C J Eagles et al 'The effects of combined treatment with betal-selective receptor antagonists and lipid-lowering drugs on fat metabolism and measures of fatigue during moderate intensity exercise a placebo-controlled study in healthy subjects page 291 - page 300
- D2) Scand J Print Health Care, Volume 17 1999, Olav Per Foss et al "Treatment of hypertensive and hypercholesterolaemic patients in general practice", page 122 - page 127
- D3) Hypertension Volume 19, No 3, 1992, James L Pool et al "Lovastatin and Coadministred Antihypertensive/ Cardiovascular Agents page 242 - page 248 page 243
- D4) Presse Med Volume 25 No 40 December 1996, S Witchitz O et al Effets comparés du captopril et de l aténolol sur le métabolisme lipidique chez des patients hypertendus hypercholesterolemiques traités par pravastatine", page 2013 - page 2016

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Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of V

- D5) Am J Health-Syst Pharm, Volume 52 August 1995, William R Garnett "Interactions with hydroxymethylglutaryl-coenzyme A reductase inhibitors", page 1639 - page 1645 page 1642, right column
- D6) WO 9802357 A1 (ASTRA AKTIEBOLAG), 22 January 1998 (22 01 98), page 7 line 25 - line 30
- D7) WO 9911260 A1 (PFIZER INC) 11 March 1999 (11 03 99), page 7, line 22 - line 26 page 18 line 22 - page 20, line 12 the claims
- D8) WO 9738694 A1 (MERCK & CO INC), 23 October 1997 (23 10 97) claims 7,14,24,29,34

Combinations of a betablocker such as metoprolol, and a cholesterol-lowering agent, such as a HMG-CoA reductase inhibitor especially a statin for the prophylactic or therapeutic treatment of for instance diseases connected with atherosclerosis, such as hypertension, hypercholesterolemia and coronary heart disease, are disclosed by inter alia documents D1) to D6) Confer as well documents D7) and D8) Thus at least claims 1, 2, 6-8, 10 11 18-20, 22, 23 26, 36-38 40 and 43 are not novel Claims 3-5 9 12-17, 21, 24 25, 39 41 and 42 are not considered to show inventive step as what is mentioned there seems to be obvious practical measures for a person skilled in the art The applicant has pointed out in the description on page 2 line 1-page 3 line 20 that some of these known combinations have certain disadvantages and that no data are disclosed for some of them or that the result is unclear However, the applicant has not shown, for the whole scope of the claims that the claimed combinations are likely to have any unexpected beneficial effects compared to those in the cited documents Confer as well the description page 8

Consequently the invention claimed in claims 1 2, 6-8, 10, 11, 18-20 22 23, 26 36-38, 40 and 43 is not novel, but the invention claimed in claims 3-5 9 12-17, 21, 24 25, 39 41 and 42 is novel The invention claimed in claims 1-26 and 36-43 is not considered to fulfil the requirement of inventive step, but is considered to fulfil the requirement of industrial applicability

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE01/00663

VI. Certain documents cited

1 Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 0038725	06 07 2000	17 12 1999	23 12 1998

Atherosclerosis, Volume 151, No 1, June 2000, G Berglund et al "(MoW3 3) Low dose metoprolol and fluvastatin slow progression of atherosclerosis Main results from BCAPS' page 1 - page 354 page 4

Atherosclerosis, Volume 151, No 1, June 2000, B Hedblad, J et al "(MoP7 W3) Low dose metoprolol and fluvastatin in silent atherosclerotic disease Metabolic and adverse effects in BCAPS" page 1 - page 354 page 24

2 Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 6, 10 14, 18, 22 and 40 are too broadly formulated. It seems unlikely that any combination covered by the claims has the properties as described in your application. It has not been shown that substantially the whole field of combinations claimed has the alleged properties and thus that inventive step exists for the whole scope of the claims. It is to be noted that the example is unclear because of the wording "statins" (page 15 line 6- 15) instead of specifying the statin used. The wordings of claims 26 and 43 are unclear. Confer PCT Article 5 and Article 6 ("Claims shall be clear and concise. They shall be fully supported by the description")

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