

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
1 August 2002 (01.08.2002)

PCT

(10) International Publication Number  
**WO 02/058731 A3**

- (51) International Patent Classification<sup>7</sup>: **A61K 45/06**, A61P 9/00, A61K 31/395
- (21) International Application Number: PCT/US02/01196
- (22) International Filing Date: 25 January 2002 (25.01.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
60/264,396 26 January 2001 (26.01.2001) US  
60/264,600 26 January 2001 (26.01.2001) US  
60/264,275 26 January 2001 (26.01.2001) US  
60/323,842 21 September 2001 (21.09.2001) US
- (71) Applicant: **SCHERING CORPORATION** [US/US]; Patent Department - K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).
- (72) Inventors: **KOSOGLOU, Teddy**; 2457 Primrose Court, Jamison, Bucks County, PA 18929-1178 (US). **RESS, Rudyard, Joseph**; 16 Tuccamirgan Road, Flemington, NJ 08822-5910 (US). **STRONY, John**; 14 Cheshire Court, Lebanon, NJ 08833 (US). **VELTRI, Enrico, P.**; 6 Toftrees Court, Princeton, NJ 08540 (US). **HAUER, William**; 70 Dock Watch Hollow Road, Warren, NJ 07059 (US).
- (74) Agent: **CANNONI, Ann, Marie**; Schering-Plough Corporation, Patent Department K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VN, YU, ZA, ZM.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Declaration under Rule 4.17:**  
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
- Published:**  
— *with international search report*
- (88) Date of publication of the international search report:  
20 November 2003
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



**WO 02/058731 A3**

(54) Title: COMBINATIONS OF STEROL ABSORPTION INHIBITOR(S) WITH CARDIOVASCULAR AGENT(S) FOR THE TREATMENT OF VASCULAR CONDITIONS

(57) Abstract: The present invention provides compositions, therapeutic combinations and methods including: (a) at least one sterol absorption inhibitor and (b) at least one cardiovascular agent different from the sterol absorption inhibitor, which can be useful for treating vascular conditions, obesity, diabetes and lowering plasma levels of sterols.

INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 02/01196

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K45/06 A61P9/00 A61K31/395

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)  
IPC 7 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)  
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, MEDLINE, EMBASE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 35277 A (SCHERING CORP) 28 December 1995 (1995-12-28) page 6; claims 6,7,9 ---	1-49
Y	THOMPSON G. R. ET AL: "Novel lipid regulating drugs" EXPERT OPINION ON INVESTIGATIONAL DRUGS, vol. 9, no. 11, November 2000 (2000-11), pages 2619-2627, XP008011782 abstract; figure 8 ---	1-49
Y	WO 00 38725 A (REITZ DAVID B ;SEARLE & CO (US); LAPPE RODNEY W (US); SCHUH JOSEPH) 6 July 2000 (2000-07-06) cited in the application page 15; claims 6-8 ---	1-49
	-/--	

Further documents are listed in the continuation of box C.  Patent family members are listed in annex.

° Special categories of cited documents :

*A* document defining the general state of the art which is not considered to be of particular relevance	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*E* earlier document but published on or after the international filing date	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y* document of particular relevance; the claimed invention cannot be considered 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.
*O* document referring to an oral disclosure, use, exhibition or other means	*&* document member of the same patent family
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search <b>28 March 2003</b>	Date of mailing of the international search report <b>15/04/2003</b>
---	---

Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer <b>Gonzalez Ramon, N</b>
--	--

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 02/01196

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	KOSOGLOU T. ET AL: "Coadministration of ezetimibe and fenofibrate leads to favorable effects on Apo CII and LDL subfractions" ATHEROSCLEROSIS, vol. 2, no. Suppl, 2001, page 89 XP001132089 abstract -----	1-49

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 02/01196**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.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 47,48 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: partially 1-49  
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 FURTHER INFORMATION sheet PCT/ISA/210
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be 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.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: partially 1-49

Present claims 2,4-10 relate to an extremely large number of possible compounds defined as sterol absorption inhibitors of Formula (I), (III)-(IX). In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity (and conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

Present claims 1, 11, 12, 16, 18, 20, 22, 24, 26, 28, 30, 33-36, 39, 40, 42,45, 47, 49 relate to compounds/compositions defined by reference to desirable characteristics or properties, namely: "sterol absorption inhibitor" (claims 1, 34,47,49); "cardiovascular agent" (claims 1, 11, 33, 47, 49); "a channel blocker" (claims 11,16); "adrenergic blocker" (claims 11,12); "adrenergic stimulant" (claims 11,20); "an angiotensin converting enzyme (ACE) inhibitor" (claims 11,18); "an antihypertensive agent" (claims 11,22); "an angiotensin II receptor antagonist" (claims 11,24); "an antianginal agent" (claims 11,26); "a coronary vasodilator" (claims 11,28); "a diuretic" (claims 11,30); "cholesterol biosynthesis inhibitor" (claim 35); "HMG CoA reductase inhibitor" (claim 36); "bile acid sequestrant" (claim 39); "an acylCoA:cholesterol O-acyltransferase inhibitor" (claim 40); "low density lipoprotein receptor activator" (claim 42); "an antioxidant" (claim 45). The claims cover all compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds/compositions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Furthermore claims 1-10, 41, 43-45, 47, 48 relate to compounds/compositions defined by reference to vague characteristics or properties, namely: "sterol absorption inhibitor prodrug" (claims 1-10,47,49); "derivatives" (claim 41); "an omega 3 fatty acid" (claim 43); "natural water soluble fiber" (claim 44); "a vitamin" (claim 45). The claims cover all compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds/compositions. Again the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, claims 1, 11, 12, 16, 18, 20, 22, 24, 26, 28, 30, 33-36, 39, 40, 42, 45, 47, 49 also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved: "sterol absorption inhibitor" (claims 1, 34,47,49); "cardiovascular agent" (claims 1, 11,33,47,49); "channel blocker" (claims 11,16); "adrenergic blocker" (claims 11,12); "adrenergic stimulant" (claims 11,20); "angiotensin converting enzyme (ACE) inhibitor" (claims 11,18); "antihypertensive agent" (claims 11,22); "an angiotensin II receptor antagonist" (claims 11,24); "antianginal agent" (claims 11,26); "coronary vasodilator" (claims 11,28); "diuretic" (claims 11,30); "cholesterol biosynthesis inhibitor" (claim 35); "HMG CoA reductase inhibitor" (claim 36); "bile acid sequestrant" (claim 39); "an

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

acylCoA:cholesterol O-acyltransferase inhibitor" (claim 40); "low density lipoprotein receptor activator" (claim 42); "antioxidant" (claim 45). Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds specifically mentioned by chemical name in claims 3,13-15,17,19,21,23,25,27,29,31,32,37,41 excluding the vague denomination of prodrug or derivative with due regard to the general idea underlying the present application

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/01196

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9535277	A	28-12-1995	AU 2943095	A 15-01-1996
			CA 2191455	A1 28-12-1995
			EP 0766667	A1 09-04-1997
			JP 10501811	T 17-02-1998
			WO 9535277	A1 28-12-1995
			US 5688785	A 18-11-1997
			-----	
WO 0038725	A	06-07-2000	AT 228012	T 15-12-2002
			AT 226448	T 15-11-2002
			AU 2157400	A 31-07-2000
			AU 2157500	A 31-07-2000
			AU 2157600	A 31-07-2000
			AU 2157700	A 31-07-2000
			AU 2157800	A 31-07-2000
			AU 2157900	A 31-07-2000
			AU 2348000	A 31-07-2000
			AU 2348100	A 31-07-2000
			AU 3103800	A 31-07-2000
			BR 9916484	A 22-01-2002
			BR 9916485	A 15-01-2002
			BR 9916486	A 05-02-2002
			BR 9916564	A 29-01-2002
			BR 9916565	A 29-01-2002
			BR 9916567	A 11-12-2001
			CA 2356156	A1 06-07-2000
			CA 2356157	A1 06-07-2000
			CA 2356158	A1 06-07-2000
			CA 2356240	A1 06-07-2000
			CA 2356422	A1 06-07-2000
			CA 2356515	A1 06-07-2000
			CA 2356607	A1 06-07-2000
			CA 2356664	A1 06-07-2000
			CN 1338944	T 06-03-2002
			CN 1338945	T 06-03-2002
			CN 1342089	T 27-03-2002
			CN 1342090	T 27-03-2002
			CN 1342091	T 27-03-2002
			CN 1338946	T 06-03-2002
			CZ 20012340	A3 14-11-2001
			CZ 20012341	A3 12-12-2001
			CZ 20012342	A3 12-12-2001
			CZ 20012343	A3 12-12-2001
			CZ 20012344	A3 16-01-2002
			CZ 20012345	A3 12-12-2001
			DE 69903661	D1 28-11-2002
			DE 69904079	D1 02-01-2003
			DK 1140190	T3 23-12-2002
			DK 1140191	T3 24-02-2003
EP 1293211	A1 19-03-2003			
EP 1140184	A1 10-10-2001			
EP 1140185	A1 10-10-2001			
EP 1140186	A1 10-10-2001			
EP 1140187	A1 10-10-2001			
EP 1140188	A1 10-10-2001			
EP 1140189	A1 10-10-2001			
EP 1140190	A1 10-10-2001			
EP 1140191	A1 10-10-2001			
-----				