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- (81) Designated States (*national*): AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.
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WO 01/13900 A3

(54) Title: COMPOSITIONS FOR THE TREATMENT OF CARDIOVASCULAR DISEASES CONTAINING PYRIDOXAL COMPOUNDS AND CARDIOVASCULAR COMPOUNDS

(57) Abstract: Methods for treating cardiovascular and related diseases such as hypertrophy, hypertension, congestive heart failure, ischemia, ischemia reperfusion injuries in various organs, arrhythmia, and myocardial infarction, are described. The methods are directed to concurrently administering a compound such as pyridoxal-5'-phosphate, pyridoxamine, pyridoxal, or a 3-acylated pyridoxal analogue with a therapeutic cardiovascular compound.

INTERNATIONAL SEARCH REPORT

Int. l. tional Application No PCT/CA 00/01020
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A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K45/06 A61P9/00

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, CHEM ABS Data, CANCERLIT, BIOSIS, EMBASE, MEDLINE, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 53606 A (MEDICURE INC) 14 September 2000 (2000-09-14) abstract page 18, paragraph 3 -page 20, paragraph 7 --- -/--	1-4,7, 10-15, 20-25, 27,30, 31, 39-48, 53,54, 56-62, 65-70, 73-78, 81,84,85

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 *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed	*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 *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 *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. *Z* document member of the same patent family
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Date of the actual completion of the international search <p style="text-align: center;">11 October 2001</p>	Date of mailing of the international search report <p style="text-align: center; font-size: 1.2em;">16/10/01</p>
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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 <p style="text-align: center;">Leherte, C</p>
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/01020

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 288 498 A (HAGUE BRIAN ET AL) 22 February 1994 (1994-02-22) claims 1,41,44,47,54,99,110,136,163,188 ---	1-4,7, 10-15, 20-25, 27,30, 31, 39-48, 53,54, 56-62, 65-70, 73-78, 81,84,85
X	WO 98 19690 A (SQUIBB BRISTOL MYERS CO) 14 May 1998 (1998-05-14) claims ---	1-4, 10-15, 18, 20-25, 30,31, 45-48, 54, 56-62, 65-70, 73-78, 84,85
X	DE 28 45 484 A (GROENING RUEDIGER) 19 October 1978 (1978-10-19) page 3, line 2 -page 4, column 13 ---	12-14, 18,20, 21, 45-47, 51,57,58
X	CA 2 123 935 A (KREAMER J W) 5 December 1994 (1994-12-05) claims ---	1-3,7, 10,11, 22-24, 27,30, 31, 39-44, 75-77, 81,84,85
X	US 5 254 572 A (SERFONTEIN WILLEM J) 19 October 1993 (1993-10-19) column 12, line 64 -column 13, line 15 --- -/--	12-14, 18,20, 21, 45-47, 51,57,58

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/01020

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>US 3 282 778 A (LOBEL MJ) 1 November 1966 (1966-11-01)</p> <p>column 1, paragraphs 1,5</p>	<p>1-3,7, 10,11, 22-24, 27,30, 31, 39-44, 75-77, 81,84,85</p>
X	<p>FR 2 641 189 A (TIMOL MAMOOJEE) 6 July 1990 (1990-07-06)</p> <p>claims</p>	<p>1-3,7, 10,11, 22-24, 27,30, 31, 39-44, 75-77, 81,84,85</p>
X	<p>VIDRIO H: "INTERACTION WITH PYRIDOXAL AS A POSSIBLE MECHANISM OF HYDRALAZINE HYPOTENSION" JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, NEW YORK, NY, US, vol. 15, no. 1, 1 January 1990 (1990-01-01), pages 150-156, XP000965625 ISSN: 0160-2446 abstract</p>	<p>12-14, 18,20, 21, 45-47, 51,57,58</p>
X	<p>VASUDEV, SINDHU C. ET AL: "Glutaraldehyde-treated bovine pericardium: changes in calcification due t vitamins and platelet inhibitors" ARTIF. ORGANS (1997), 21(9), 1007-1013 , 1997, XP001004729</p> <p>page 1011, column 1, paragraph 2 -page 1012, column 2</p>	<p>1-3,7, 10,11, 22-24, 27,30, 31, 39-44, 75-77, 81,84,85</p>
A	<p>FOLSOM A R ET AL: "PROSPECTIVE STUDY OF CORONARY HEART DISEASE INCIDENCE IN RELATION TO FASTING TOTAL HOMOCYSTEINE, RELATED GENETIC POLYMORPHISMS, AND B VITAMINS THE ATHEROSCLEROSIS RISK IN COMMUNITIES (ARIC) STUDY" CIRCULATION, AMERICAN HEART ASSOCIATION, DALLAS, TX, US, vol. 98, no. 3, 21 July 1998 (1998-07-21), pages 204-210, XP000965312 ISSN: 0009-7322 abstract</p>	<p>1-4,7, 10-15, 20-25, 27,30, 31, 39-48, 53,54, 56-62, 65-70, 73-78, 81,84,85</p>

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/01020

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>RIMM E B ET AL: "FOLATE AND VITAMIN B6 FROM DIET AND SUPPLEMENTS IN RELATION TO RISK OF CORONARY HEART DISEASE AMONG WOMEN" JAMA THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, CHICAGO, IL, US, vol. 279, no. 5, 4 February 1998 (1998-02-04), pages 359-364, XP000965325 ISSN: 0098-7484</p> <p>the whole document</p>	<p>1-4,7, 10-15, 20-25, 27,30, 31, 39-48, 53,54, 56-62, 65-70, 73-78, 81,84,85</p>
A	<p>KUBYSHKIN V F ET AL: "Comparative characteristics of the arrhythmic syndrome and the possibility for its coenzyme correction in dilated and hypertrophic cardiomyopathy. S ravnitel'naia kharakteristika aritmicheskogo sindroma i vozmozhnosti ego kofermentnoi korrektsii pri dilatatsionnoi i gipertroficheskoj kardiomiopatii" TERAPEVTICHESKII ARKHIV - THERAPEUTIC ARCHIVES, MOSCOW, RU, vol. 61, no. 9, 1989, pages 82-85, XP000965693 ISSN: 0040-3660 page 85, column 2, paragraph 2</p>	<p>1-4,7, 10-15, 20-25, 27,30, 31, 39-48, 53,54, 56-62, 65-70, 73-78, 81,84,85</p>
A	<p>AYBAK M ET AL: "EFFECT OF ORAL PYRIDOXINE HYDROCHLORIDE SUPPLEMENTATION ON ARTERIAL BLOOD PRESSURE IN PATIENTS WITH ESSENTIAL HYPERTENSION" ARZNEIMITTEL FORSCHUNG. DRUG RESEARCH, EDITIO CANTOR. AULENDORF, DE, vol. 45, no. 112, 1995, pages 1271-1273, XP000961002 ISSN: 0004-4172</p> <p>page 1271, column 1, paragraph 1</p>	<p>1-4,7, 10-15, 20-25, 27,30, 31, 39-48, 53,54, 56-62, 65-70, 73-78, 81,84,85</p>
A	<p>LEVY H A ET AL: "PYRIDOXINE DEFICIENCY IN CONGESTIVE HEART FAILURE (25037)" PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY & MEDICINE, WILLIAMS AND WILKINS, XX, vol. 101, August 1959 (1959-08), pages 617-621, XP000965627 ISSN: 0037-9727</p> <p>page 620, column 2, paragraph 2 -page 621, column 1</p>	<p>1-4,7, 10-15, 20-25, 27,30, 31, 39-48, 53,54, 56-62, 65-70, 73-78, 81,84,85</p>

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/01020

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>EP 0 270 026 A (VESTA MED PTY LTD) 8 June 1988 (1988-06-08)</p> <p>abstract</p> <p style="text-align: center;">-----</p>	<p>1-4, 10-15, 20-25, 30, 31, 45-48, 51, 54, 56-62, 65-70, 73-78, 84, 85</p>

INTERNATIONAL SEARCH REPORT

International application No.
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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 all claims 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.:
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:

see additional sheet

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.:

1 4 8
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

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-3, 10-14, 20-24, 30, 31, 45-47, 57-61, 65-69, 73-77, 84, 85 (all partially), 4, 15, 25, 48, 54, 56, 62, 70, 78

Pharmaceutical combination for the treatment of cardiovascular and related diseases comprising pyridoxal-5'-phosphate, pyridoxal, pyridoxamine or a 3-acylated pyridoxal analogue and an angiotensin converting enzyme inhibitor.

2. Claims: 1-3, 10-14, 20, 21, 59-61, 65-69, 73-77, 84, 85 (all partially), 5, 16, 63, 71, 79

Pharmaceutical combination for the treatment of cardiovascular and related diseases comprising pyridoxal-5'-phosphate, pyridoxal, pyridoxamine or a 3-acylated pyridoxal analogue and an angiotensin II receptor antagonist (as far as not comprised in invention 1).

3. Claims: 1-3, 10-14, 20-24, 30-34, 37, 38, 45-47, 57-61, 65-69, 73-77, 84, 85 (all partially), 6, 17, 26, 35, 49, 64, 72, 80

Pharmaceutical combination for the treatment of cardiovascular and related diseases comprising pyridoxal-5'-phosphate, pyridoxal, pyridoxamine or a 3-acylated pyridoxal analogue and a calcium channel blocker (as far as not comprised in invention 1-2).

4. Claims: 1-3, 10, 11, 22-24, 30, 31, 75-77, 84, 85 (all partially), 7, 27, 39-44, 81

Pharmaceutical combination for the treatment of cardiovascular and related diseases comprising pyridoxal-5'-phosphate, pyridoxal, pyridoxamine or a 3-acylated pyridoxal analogue and an antithrombolytic agent (as far as not comprised in invention 1-3).

5. Claims: 1-3, 10-11, 22-24, 30-34, 37, 38, 45-47, 57, 58, 75-77, 84, 85 (all partially), 8, 28, 36, 50, 82

Pharmaceutical combination for the treatment of cardiovascular and related diseases comprising

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

pyridoxal-5'-phosphate, pyridoxal, pyridoxamine or a 3-acylated pyridoxal analogue and a beta-adrenergic receptor antagonist (as far as not comprised in invention 1-4).

6. Claims: 1-3, 10-14, 20-24, 30, 31, 45-47, 57, 58, 75-77, 84, 85 (all partially), 9, 19, 29, 52, 55, 83

Pharmaceutical combination for the treatment of cardiovascular and related diseases comprising pyridoxal-5'-phosphate, pyridoxal, pyridoxamine or a 3-acylated pyridoxal analogue and a diuretic (as far as not comprised in invention 1-5).

7. Claims: 1-3, 10, 11, 22-24, 30, 31, 45-47, 57, 58, 75-77, 84, 85 (all partially), 53

Pharmaceutical combination for the treatment of cardiovascular and related diseases comprising pyridoxal-5'-phosphate, pyridoxal, pyridoxamine or a 3-acylated pyridoxal analogue and an alpha-adrenergic receptor antagonist (as far as not comprised in invention 1-6).

8. Claims: 12-14, 20, 21, 45-47, 57, 58 (all partially), 18, 51

Pharmaceutical combination for the treatment of cardiovascular and related diseases comprising pyridoxal-5'-phosphate, pyridoxal, pyridoxamine or a 3-acylated pyridoxal analogue and a vasodilator (as far as not comprised in invention 1-7).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4, 7, 10-15, 18, 20-25, 27, 30, 31, 39-44, 45-48, 51, 54, 56-62, 65-70, 73-78, 81, 84, 85

Present claims 1-4, 7, 10-15, 18, 20-25, 27, 30, 31, 39-44, 45-48, 51, 54, 56-62, 65-70, 73-78, 81, 84 and 85 relate to compounds defined (inter alia) by reference to the following parameters: "3-acylated pyridoxal analogue", "angiotensin converting enzyme inhibitor", "antithrombolytic agent" and "vasodilator".

The claims cover all compounds having those characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. 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. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search for the inventions 1, 4 and 8 has been restricted to the compounds individually structurally identified by name in the claims, with due regard to the therapeutic applications mentioned in the claims.

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/CA 00/01020

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0053606	A	14-09-2000	AU 3183400 A WO 0053606 A1
			28-09-2000 14-09-2000
US 5288498	A	22-02-1994	CA 1338978 A1 US 4863737 A US 4671953 A AT 138562 T AU 642664 B2 AU 6337190 A CA 2066403 A1 DE 69027216 D1 DE 69027216 T2 DK 490944 T3 EP 0490944 A1 ES 2089027 T3 JP 2749198 B2 JP 5500058 T NO 920858 A WO 9103236 A1 US 5855908 A AT 116131 T CA 1271421 A1 CA 1339190 A1 DE 3650189 D1 DE 3650189 T2 EP 0200490 A2 EP 0487520 A1 EP 0490891 A1 EP 0404205 A1 US 4885173 A WO 9103099 A1 WO 9103234 A1 US 5484602 A US 5132114 A US 5122127 A US 5288497 A US 5783207 A US 5785989 A AT 61729 T DE 3678195 D1
			11-03-1997 05-09-1989 09-06-1987 15-06-1996 28-10-1993 08-04-1991 06-03-1991 04-07-1996 17-10-1996 21-10-1996 24-06-1992 01-10-1996 13-05-1998 14-01-1993 04-03-1992 21-03-1991 05-01-1999 15-01-1995 10-07-1990 29-07-1997 09-02-1995 04-05-1995 05-11-1986 03-06-1992 24-06-1992 27-12-1990 05-12-1989 07-03-1991 21-03-1991 16-01-1996 21-07-1992 16-06-1992 22-02-1994 21-07-1998 28-07-1998 15-04-1991 25-04-1991
WO 9819690	A	14-05-1998	AU 719290 B2 AU 5244298 A EP 0951293 A1 JP 2001504104 T WO 9819690 A1 US 6127370 A US 6008221 A
			04-05-2000 29-05-1998 27-10-1999 27-03-2001 14-05-1998 03-10-2000 28-12-1999
DE 2845484	A	30-04-1980	DE 2845484 A1
			30-04-1980
CA 2123935	A		NONE
US 5254572	A	19-10-1993	US 5631271 A EP 0379936 A2 JP 2237921 A ZA 9000319 A
			20-05-1997 01-08-1990 20-09-1990 25-09-1991

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 00/01020

Patent document cited in search report	Publication date	Publication date	Patent family member(s)	Publication date
US 3282778	A	01-11-1966	NONE	
<hr style="border-top: 1px dashed black;"/>				
FR 2641189	A	06-07-1990	FR 2641189 A1	06-07-1990
			WO 9119500 A1	26-12-1991
<hr style="border-top: 1px dashed black;"/>				
EP 0270026	A	08-06-1988	AU 8169087 A	02-06-1988
			EP 0270026 A2	08-06-1988
			JP 63145229 A	17-06-1988
			NZ 222664 A	26-06-1990
			US 5631271 A	20-05-1997
			ZA 8708981 A	25-04-1990
<hr style="border-top: 1px dashed black;"/>				