

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
24 April 2003 (24.04.2003)

PCT

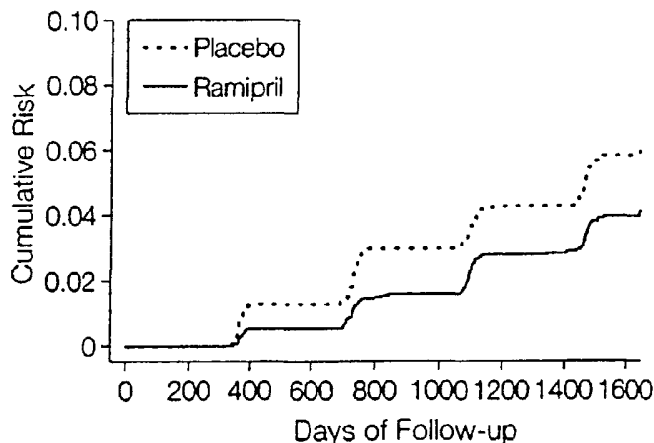
(10) International Publication Number
WO 03/032965 A3

- (51) International Patent Classification⁷: **A61K 31/403**,
A61P 1/18, 3/10, 5/50, A61K 31/38, 31/00 [US/US]; 4136 NW 88th Ave., Apt. #107, Coral Springs, FL 33065 (US).
- (21) International Application Number: PCT/US02/33213
- (22) International Filing Date: 17 October 2002 (17.10.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/344,495 17 October 2001 (17.10.2001) US
- (71) Applicant (for all designated States except US): **KING PHARMACEUTICALS RESEARCH AND DEVELOPMENT, INC** [US/US]; 7001 Weston Parkway, Suite 300, Cary, NC 27513 (US).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): **YUSUF, Salim**
- (74) Agent: **MANSO, Peter, J.**; Edwards & Angell, 350 East Las Olas Blvd., Suite 1150, Ft. Lauderdale, FL 33301 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, 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, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (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, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,

[Continued on next page]

(54) Title: USE OF ACE INHIBITORS FOR REDUCING TYPE 2 DIABETES IN HIGH RISK PATIENTS

Development of Diabetes:
Ramipril vs Placebo



No. at Risk										
Placebo	2883	2867	2800	2765	2682	2645	2571	2497	1279	
Ramipril	2837	2807	2772	2725	2672	2635	2571	2528	1317	

(57) Abstract: The present invention relates to the use of an angiotensin-converting enzyme inhibitor, such as ramipril, to reduce or prevent Type 2 diabetes in high risk patients. The present invention also relates the use of an angiotensin-converting enzyme inhibitor, such as ramipril, to reduce the decline of β -cell function, increase islet blood flow, lower aldosterone secretion, lower renal potassium wasting, increase pancreatic β -cell perfusion, reduce insulin resistance in skeletal muscles, and increase insulin-mediated glucose disposal and uptake by skeletal muscles.

The relative risk for developing diabetes among patients taking ramipril vs placebo is 0.66 (95% confidence interval, 0.51-0.85; $P < .001$).

WO 03/032965 A3



TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designation US*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designation US*
- *of inventorship (Rule 4.17(iv)) for US only*

Published:

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:

27 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.

INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 02/33213

A. CLASSIFICATION OF SUBJECT MATTER		
IPC 7	A61K31/403	A61P1/18 A61P3/10 A61P5/50 A61K31/38 A61K31/00
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) WPI Data, EPO-Internal, PAJ, EMBASE, BIOSIS, MEDLINE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YUSUF S ET AL: "Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators." THE NEW ENGLAND JOURNAL OF MEDICINE. UNITED STATES 20 JAN 2000, vol. 342, no. 3, 20 January 2000 (2000-01-20), pages 145-153, XP008013952 ISSN: 0028-4793 page 150, column 1, paragraph 2 table 4 --- -/--	1-17
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
° Special categories of cited documents :		
<p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*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)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p>		<p>*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</p> <p>*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</p> <p>*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.</p> <p>* & * document member of the same patent family</p>
Date of the actual completion of the international search 25 September 2003		Date of mailing of the international search report 08/10/2003
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 Strack, E

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/33213

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>WO 01 15674 A (AVENTIS PHARMA GMBH) 8 March 2001 (2001-03-08) page 3, line 18 - line 22 page 7, line 11 - line 16 example 6 page 24, line 17 - line 18 page 27, line 19 - line 22</p>	1-17
X	<p>WO 01 15673 A (AVENTIS PHARMA GMBH) 8 March 2001 (2001-03-08) page 1, line 6 - line 12 page 4, line 28 claims 3,12</p>	1-17
X	<p>EP 0 331 014 A (THERA GES FUER PATENTE) 6 September 1989 (1989-09-06) column 1, line 1-4,23-27 claims 1,2</p>	1-17
X	<p>JANKA H U ET AL: "Metabolic effects of ramipril treatment in hypertensive subjects with non-insulin-dependent diabetes mellitus." ARZNEIMITTEL-FORSCHUNG. GERMANY, WEST APR 1990, vol. 40, no. 4, April 1990 (1990-04), pages 432-435, XP001109698 ISSN: 0004-4172 abstract</p>	1-17
X	<p>"Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators." LANCET. ENGLAND 22 JAN 2000, vol. 355, no. 9200, 22 January 2000 (2000-01-22), pages 253-259, XP002232380 ISSN: 0140-6736 abstract</p>	1-11
Y	<p>abstract</p>	12-17
X	<p>KRUETZFELDT JAN ET AL: "Ramipril increases the protein level of skeletal muscle IRS-1 and alters protein tyrosine phosphatase activity in spontaneously hypertensive rats." NAUNYN-SCHMIEDEBERG'S ARCHIVES OF PHARMACOLOGY, vol. 362, no. 1, July 2000 (2000-07), pages 1-6, XP001148413 ISSN: 0028-1298 abstract</p>	1,8-10
	--- -/--	

INTERNATIONAL SEARCH REPORT

ational Application No
PCT/US 02/33213

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GALLETTI FERRUCCIO ET AL: "Controlled study of the effect of angiotensin converting enzyme inhibition versus calcium-entry blockade on insulin sensitivity in overweight hypertensive patients: Trandolapril Italian Study (TRIS)." JOURNAL OF HYPERTENSION, vol. 17, no. 3, March 1999 (1999-03), pages 439-445, XP008014000 ISSN: 0263-6352 page 444, column 1, line 36 - line 39 abstract ----	1,8-10
X	DE 43 08 504 A (KNOLL AG) 22 September 1994 (1994-09-22) claim 1 ---	1,8-10
X	KEILANI T ET AL: "Selected aspects of ACE inhibitor therapy for patients with renal disease: impact on proteinuria, lipids and potassium." JOURNAL OF CLINICAL PHARMACOLOGY. UNITED STATES JAN 1995, vol. 35, no. 1, January 1995 (1995-01), pages 87-97, XP008021110 ISSN: 0091-2700 abstract ---	18
Y	abstract ---	19
X	BAKRIS GEORGE L ET AL: "ACE inhibition or angiotensin receptor blockade: Impact on potassium in renal failure." KIDNEY INTERNATIONAL, vol. 58, no. 5, November 2000 (2000-11), pages 2084-2092, XP001164193 ISSN: 0085-2538 abstract ---	18
Y	abstract ---	19
X	MUTSCHLER: "Arzneimittelwirkungen" , WVG , STUTTGART XP002232383 page 576, column 1, paragraph 1 figures B4-27 tables B4-29 page 579, column 1, paragraph 3 ---	18,19
Y	figures B4-27 tables B4-29 page 579, column 1, paragraph 3 ---	12-17
X	CARLSSON P O ET AL: "Angiotensin II and the endocrine pancreas: effects on islet blood flow and insulin secretion in rats." DIABETOLOGIA. GERMANY FEB 1998, vol. 41, no. 2, February 1998 (1998-02), pages 127-133, XP001148412 ISSN: 0012-186X abstract ---	12,14,16
	----- -/--	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/33213

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	YUSUF S ET AL: "RAMIPRIL AND THE DEVELOPMENT OF DIABETES" JAMA THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, CHICAGO, IL, US, vol. 286, no. 15, 17 October 2001 (2001-10-17), pages 1882-1885, XP008013945 ISSN: 0098-7484 abstract page 1885, column 1, paragraph 3 -column 2, paragraph 2 -----	1-19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/33213

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 1-19 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:

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

Present claims 1, 2, 5-10, 12, 14, 16 and 18 relate to a large number of possible compounds ("angiotensin converting enzyme inhibitor"). Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. 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, present claims 12-19 relate to the treatment of diseases which are actually not well defined. The claims cover all uses relating to the terms "slowing or reversing the decline of beta-cell function" (claims 12 and 13), "increasing islet blood flow" (claims 14 and 15), "increasing pancreatic beta-cell perfusion" (claims 16 and 17) and "lowering aldosterone secretion and renal potassium wasting" (claims 18 and 19) whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for diabetes, only.

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole scope of the claims is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define uses by reference to mechanistic terms which do not allow any practical application in the form of a defined, real treatment of a pathological condition. This lack of clarity in the present case is such as to render a meaningful search over the whole scope of the claims impossible.

Consequently, the search has been carried out for those parts of the application which do appear to be clear, supported and disclosed, namely the use of ramipril in relation to the treatment and prevention of diabetes.

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 02/33213

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0115674	A	08-03-2001	AU 7649100 A	26-03-2001
			BG 106360 A	31-10-2002
			BR 0013704 A	07-05-2002
			CA 2382549 A1	08-03-2001
			CN 1368881 T	11-09-2002
			CZ 20020770 A3	12-06-2002
			EE 200200086 A	15-04-2003
			WO 0115674 A2	08-03-2001
			EP 1216038 A2	26-06-2002
			HU 0203326 A2	28-02-2003
			NO 20020978 A	18-04-2002
			SK 2692002 A3	02-07-2002
			TR 200200515 T2	21-11-2002
			WO 0115673	A
BG 106319 A	29-12-2002			
BR 0013540 A	30-04-2002			
CA 2382387 A1	08-03-2001			
CN 1384756 T	11-12-2002			
CZ 20020644 A3	15-05-2002			
EE 200200085 A	15-04-2003			
WO 0115673 A2	08-03-2001			
EP 1212081 A2	12-06-2002			
HU 0202461 A2	28-12-2002			
JP 2003508426 T	04-03-2003			
NO 20020850 A	21-02-2002			
SK 2702002 A3	10-09-2002			
TR 200200518 T2	21-06-2002			
TR 200202463 T2	21-01-2003			
TR 200202464 T2	21-01-2003			
TR 200202466 T2	23-12-2002			
TR 200202467 T2	23-12-2002			
EP 0331014	A	06-09-1989	AU 3091889 A	07-09-1989
			DK 99989 A	03-09-1989
			EP 0331014 A2	06-09-1989
			JP 1261334 A	18-10-1989
DE 4308504	A	22-09-1994	DE 4308504 A1	22-09-1994
			AU 6376694 A	11-10-1994
			WO 9421285 A1	29-09-1994