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A61K 31/426, 31/427 Abbott Park Road, Abbott Park, IL 60064-6008 (US).
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10/325,420 20 December 2002 (20.12.2002) US 25 November 2004
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60061 (US).

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- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

*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.*

(54) Title: TREATMENT OF CHRONIC HEART FAILURE

(57) Abstract: Methods of treating chronic heart failure (CHF) by increasing the high energy phosphate concentrations available to heart muscle by administering a xanthine oxidase inhibitor to a patient having CHF are provided. As a result of such therapy, contractility of the heart is improved.



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/39410

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 A61P9/04 A61K31/426 A61K31/427				
According to International Patent Classification (IPC) or to both national classification and IPC				
<b>B. FIELDS SEARCHED</b>				
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, MEDLINE, CHEM ABS Data, EMBASE, BIOSIS, WPI Data, PAJ				
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>				
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	WO 00/53224 A (MAX DELBRUECK CENTRUM ; RAUCHHAUS MATHIAS (DE); ANKER STEFAN (DE);) 14 September 2000 (2000-09-14) claims 1,26	1		
A	----- ANKER, S.D.: "Peripheral circulation, skeletal muscle and cachexia" A NEW LOOK AT THE HEART IN HEART FAILURE, [Online] 26 October 2001 (2001-10-26), - 27 October 2001 (2001-10-27) pages 1-47, XP002278501 Lisbon-Portugal Retrieved from the Internet: URL: <a href="http://me.merck.de/EMD/UK/UKNEWS.NSF/0/9301b28538413a73c1256af8003c3afe/\$FILE/AbstractsLisbon.pdf">http://me.merck.de/EMD/UK/UKNEWS.NSF/0/9301b28538413a73c1256af8003c3afe/\$FILE/AbstractsLisbon.pdf</a> [retrieved on 2004-04-27] page 10 ----- -/--	1-4		
<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 :				
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;">                     "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                 </td> <td style="width: 50%; border: none; vertical-align: top;">                     "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.                      "&amp;" document member of the same patent family                 </td> </tr> </table>			"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. "&" document member of the same patent family
"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. "&" document member of the same patent family			
Date of the actual completion of the international search  <p style="text-align: center; font-size: 1.2em;">29 April 2004</p>		Date of mailing of the international search report  <p style="text-align: center; font-size: 1.2em;">- 5. 10. 2004</p>		
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; font-size: 1.2em;">Langer, O</p>		

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/39410

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>N.N.: "GOUT DRUG SHOWS PROMISE IN TREATING CHRONIC HEART FAILURE" AMERICAN HEART ASSOCIATION, [Online] 18 June 2002 (2002-06-18), pages 1-2, XP002278502 Retrieved from the Internet: URL:http://www.sciencedaily.com/releases/2002/06/020618072846.htm&gt; [retrieved on 2004-04-27] paragraph [0002] - paragraph [0007]</p> <p>-----</p>	1-4
A	<p>DOEHNER WOLFRAM ET AL: "Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies." CIRCULATION. UNITED STATES 4 JUN 2002, vol. 105, no. 22, 4 June 2002 (2002-06-04), pages 2619-2624, XP002278503 abstract page 2619, left-hand column, paragraph 1 - page 2620, column T, paragraph 1</p> <p>-----</p>	1-4
A	<p>US 6 489 476 B1 (KASIBHATLA SRINIVAS RAO ET AL) 3 December 2002 (2002-12-03) example 27</p> <p>-----</p>	1-4

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 03/39410

## 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 1-4 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 compounds.
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.:
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.:  
  
1-4 (all partially)

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

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

1. claims: 1-4 (all partially)

Use of a xanthine oxidase inhibitor according to general formula (I) where Ar represents an unsubstituted or substituted furyl group and pharmaceutically acceptable salts thereof in the manufacture of a medicament for increasing cardiac contractility in a chronic heart failure (CHF) patient, for increasing high energy phosphate concentrations in the heart muscle of a patient having CHF, and for the treatment of CHF; method to increase cardiac contractility in a CHF patient, to increase high energy phosphate concentrations in the heart muscle of a patient having CHF, and to treat CHF using said xanthine oxidase inhibitor.

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2. claims: 1-4 (all partially)

Use of a xanthine oxidase inhibitor according to general formula (I) where Ar represents a group according to formula (II) and pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment of chronic heart failure (CHF); method to treat CHF using said xanthine oxidase inhibitor.

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3. claims: 1-4 (all partially)

Use of a xanthine oxidase inhibitor according to general formula (I) where Ar represents a group according to formula (II) and pharmaceutically acceptable salts thereof in the manufacture of a medicament for increasing cardiac contractility in a chronic heart failure (CHF) patient and for increasing high energy phosphate concentrations in the heart muscle of a patient having CHF, as far as not part of invention 2; method to increase cardiac contractility in a CHF patient and for increasing high energy phosphate concentrations in the heart muscle of a patient having CHF using said xanthine oxidase inhibitor, as far as not part of invention 2.

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Continuation of Box I.1

Although claims 1-4 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 compounds.

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Continuation of Box I.2

Claims Nos.: -

1) Present claims 1-3 relate to an extremely large number of possible compounds, namely the functionally defined group of xanthine oxidase inhibitors. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed, namely the compounds according to formula (I) and pharmaceutically acceptable salts thereof.

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.

The claims encompass a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function has not been defined. In the absence of such a relationship either disclosed in the as-filed application or recognisable by one skilled in the art based upon information readily available, the skilled artisan would not know how to make and use compounds that lack a structural definition.

2) The expression "increasing high energy phosphate concentrations in heart muscle of a patient having CHF" in claim 2 is considered to be unclear under Article 6 PCT with respect to the therapeutical effect to be achieved. Based on the disclosure in the description on page 5, lines 11 and 12 of the description, this expression has been interpreted and searched as relating to the provision of high energy phosphates in order to increase the cardiac contractility in a CHF patient.

3) Consequently, the search has been carried out for those parts of the claims which relate to invention 1 and appear to be sufficiently supported and disclosed, namely for the use of the compounds according to formula (I) where Ar is an unsubstituted or substituted furyl group or of pharmaceutically acceptable salts thereof in the manufacture of a medicament for increasing cardiac contractility in a CHF patient, for increasing high energy phosphate concentrations in the heart muscle of a patient having CHF (in the above-defined meaning), and for the treatment of chronic heart failure (CHF).

4) It has been assumed that corrupted lines 5 and 6 of claim 4 ("wherein R1, R2, and R3 (...) from 1 to 2, R4, R5") should read corresponding to page 8, lines 12 and 13 of the description.

The applicant's attention is drawn to the fact that 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. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/39410

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