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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: COMPOSITIONS AND METHODS FOR TREATING OPIATE INTOLERANCE

(57) Abstract: Provided are compositions comprising an opiate analgesic and an active compound containing the R isomer of N-methylnalorphine in a pharmaceutically acceptable carrier. Also provided are methods of treating opiate intolerance by administration of an active compound containing R N-methylnalorphine or a pharmaceutically acceptable salt thereof. The active compound may be administered either acutely or chronically to subjects receiving opiate treatment. Further provided are methods of inducing analgesia by administering to a subject an opiate analgesic concurrently with an active compound containing R N-methylnalorphine or a pharmaceutically acceptable salt thereof.

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INTERNATIONAL SEARCH REPORT

Int: ional Application No
PCT/US 00/23264

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/485 A61K31/166 A61K31/4178 A61K31/439 A61K31/4468
A61P25/36

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, CHEM ABS Data, BIOSIS, CANCERLIT, AIDSLINE, MEDLINE, SCISEARCH, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NOTARNICOLA A. ET AL: "Relative ability of N- methyl nalorphine and N-methyl levallorphan to prevent antinociception and intestinal transit inhibition in morphine treated rats." LIFE SCIENCES, (1983) 33/SUPPL. 1 (481-484). CODEN: LIFSAK, XP000980614	1-10, 13-21,23
Y	the whole document --- -/--	1-10, 13-21, 23-25, 28-31

☒ 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.
- *&* document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

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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>BIANCHETTI A. ET AL: "Quaternary derivatives of narcotic antagonists: Stereochemical requirements at the chiral nitrogen for in vitro and in vivo activity." LIFE SCIENCES, (1983) 33/SUPPL. 1 (415-418). CODEN: LIFSAK, XP000980615 abstract page 416, paragraph 2 table I page 418, paragraph 2 - paragraph 3 ---</p>	<p>1-10, 13-21, 23</p>
X	<p>CLARK S J ET AL: "EVALUATION OF OPIOID-INDUCED ANTINOCICEPTIVE EFFECTS IN ANESTHETIZED AND CONSCIOUS ANIMALS" BRITISH JOURNAL OF PHARMACOLOGY, vol. 95, no. 1, 1988, pages 275-283, XP000980392 ISSN: 0007-1188 cited in the application page 278, column 2, paragraph 1 -page 279, column 1, paragraph 1 tables 2,3 page 281, column 1, paragraph 1 page 281, column 2, paragraph 1 ---</p>	<p>1-10, 13-21</p>
X	<p>FERREIRA S H ET AL: "IS METHYL NALORPHINIUM THE PROTOTYPE OF AN IDEAL PERIPHERAL ANALGESIC" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 99, no. 1, 1984, pages 23-30, XP000980657 ISSN: 0014-2999 abstract page 23, column 2, paragraph 2 -page 24, column 1, paragraph 1 page 25, column 2, paragraph 1 -page 27, column 1, paragraph 1 figure 3 table 1 page 27, column 2, paragraph 2 -page 28, column 1, paragraph 3 --- -/--</p>	<p>1-10, 13-21, 23-25, 28-31</p>

INTERNATIONAL SEARCH REPORT

International Application No

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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>EP 0 113 632 A (SANOFI SA) 18 July 1984 (1984-07-18)</p> <p>abstract page 1, line 4 - line 18 page 1, line 28 -page 2, line 21 page 3, line 15 - line 23 page 6, line 1 -page 7, line 5 page 8, line 1 - line 5 example 1 claims 1,4-7</p> <p style="text-align: center;">---</p>	<p>1-10, 13-21, 23-25, 28-31</p>
Y	<p>US 4 719 215 A (GOLDBERG LEON I) 12 January 1988 (1988-01-12)</p> <p>abstract column 1, line 6 - line 41 column 2, line 37 - line 47 column 3, line 1 - line 25 claims</p> <p style="text-align: center;">---</p>	<p>1-10, 13-21, 23-25, 28-31</p>
Y	<p>WO 99 22737 A (ARCH DEV CORP ;DRELL WILLIAM (US); FOSS JOSEPH F (US); MOSS JONATH) 14 May 1999 (1999-05-14)</p> <p>abstract example 1 claims page 2, line 14 - line 32 page 3, line 11 -page 4, line 5 page 1, line 17 - line 22</p> <p style="text-align: center;">---</p>	<p>1-10, 13-21,23</p>
Y	<p>KIANG J.G. ET AL: "Tolerance to morphine bradycardia in the rat." JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1983) 226/1 (187-191). CODEN: JPETAB, XP000980656</p> <p>abstract page 188, column 2, paragraph 3 page 190, column 1, paragraph 5</p> <p style="text-align: center;">---</p>	<p>1-10, 13-21,23</p>
A	<p>US 5 756 514 A (LARIJANI GHASSEM E) 26 May 1998 (1998-05-26)</p> <p>abstract column 1, line 10 - line 19 column 1, line 55 - line 63 column 2, line 28 - line 43 column 3, line 52 -column 4, line 16 claims</p> <p style="text-align: center;">-----</p>	<p>1-7, 9-11, 13-19, 21-23, 25-32</p>

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 11, 12, 22, 26, 27, 32 relate to a compound defined by reference to a desirable characteristic or property, namely "an anti-emetic compound", and " a serotonin receptor antagonist". The claims cover all compounds having this characteristic or property, 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 compound by reference to a result to be achieved. 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 in the description on p. 12, lines 23-25 and on p. 18 (Table 2).

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

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0113632 A	18-07-1984	FR 2538805 A CA 1220200 A JP 59130871 A	06-07-1984 07-04-1987 27-07-1984
US 4719215 A	12-01-1988	EP 0306575 A US 4861781 A AT 78687 T DE 3780819 D DE 3780819 T GR 3005834 T	15-03-1989 29-08-1989 15-08-1992 03-09-1992 14-01-1993 07-06-1993
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US 5756514 A	26-05-1998	NONE	