(54) Title: OPIOID ANTAGONISTS CONTAINING COMPOSITIONS FOR ENHANCING ANALGESIC POTENCY OF TRAMADOL AND ATTENUATING ITS ADVERSE SIDE EFFECTS

(57) Abstract: The invention generally relates to compositions and methods with tramadol and an opioid antagonist to enhance analgesic potency and/or attenuate one or more adverse effects of tramadol, including adverse side effect(s) in humans such as nausea, vomiting, dizziness, headache, sedation (somnolence) or pruritus. This invention relates to compositions and methods for selectively enhancing the analgesic potency of tramadol and simultaneously attenuating anti-analgesia, hyperalgesia, hyperexcitability, physical dependence and/or tolerance effects associated with the administration of tramadol. The methods of the present invention comprise administering to a subject an analgesic or subanalgesic amount of tramadol and an amount of excitory opioid receptor antagonist such as naltrexone or nalmefene effective to enhance the analgesic potency of tramadol and attenuate the anti-analgesia, hyperalgesia, hyperexcitability, physical dependence and/or tolerance effects of tramadol.

[Continued on next page]
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, 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), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(88) Date of publication of the international search report: 25 January 2001

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Published:
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INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
PCl 7 A61K31/485 // (A61K31/485,31:135)

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)
BIOSIS, CHEM ABS Data, EPO-Internal, CANCERLIT, EMBASE, MEDLINE, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
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<tbody>
<tr>
<td>X</td>
<td>MARCUS, K. T. ET AL: &quot;Naloxone does not reverse tramadol-induced suppression of formalin-evoked pain behavior or spinal cord fos expression in the rat&quot;</td>
<td>1, 2, 4, 8-10, 12, 16-18, 20, 24, 25, 28, 30-32, 35, 37-39, 42, 44, 45, 48, 50-52, 55, 57, 58, 61</td>
</tr>
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the whole document

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search: 30 October 2000
Date of mailing of the international search report: 07/11/2000

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## INTERNATIONAL SEARCH REPORT

### DOCUMENTS CONSIDERED TO BE RELEVANT

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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>
| X        | COLLART, L. ET AL: "Partial inhibition of tramadol antinociceptive effect by naloxone in man."
| X        | SPILLER, HENRY A. (I) ET AL: "Prospective multicenter evaluation of tramadol exposure."
|          | page 363, column 2, paragraph 3 - paragraph 4 | |
| X        | DESMEULES, J. A. ET AL: "Contribution of monoaminergic modulation to the analgesic effect of tramadol"
BR. J. CLIN. PHARMACOL. (1996), 41(1), 7-12 , XP000950042 | 1, 2, 4, 8-10, 12, 16-18, 20, 24, 25, 28, 30-32, 35, 37-39, 42, 44, 45, 48, 50-52, 55, 57, 58, 61 |
|          | abstract | |

Form PCT/ISA/210 (continuation of second sheet) (July 1992)
Continuation of Box I.2

Claims Nos.: 1, 2, 6-10, 14-18, 22-24, 28-31, 35-38, 42-44, 48-51, 55-57, 61-64, 68-72, 75, 76.

Present claims 1, 2, 6-10, 14-18, 22-24, 28-31, 35-38, 42-44, 48-51, 55-57, 61-64, 68-72, 75 and 76 relate to a compound defined by reference to a desirable characteristic or property, namely "an excitatory opioid receptor antagonist" or "similarly acting opioid alkaloid and opioid peptide". 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 opioid receptor antagonists specifically defined in the claims, with due regard to the general idea underlying the 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.