Title: MODIFIED RELEASE COMPOSITIONS OF MILNACIPRAN

Abstract: A once-a-day oral milnacipran modified release formulation has been developed. The formulation comprises an extended release dosage unit (Optionally containing the immediate release portion) coated with delayed release coating. The milnacipran composition, when administered orally, first passes through the stomach releasing from zero to less than 10% of the total milnacipran dose and then enters the intestines where drug is released slowly over an extended period of time. The release profile is characterized by a 0.05-4 hours lag time period during which less than 10% of the total milnacipran dose is released followed by a slow or extended release of the remaining drug over a defined period of time. The composition provides in vivo drug plasma levels characterized by T_{max} 4-10 hours and an approximately linear drop-off thereafter and C_{max} below 3000 ng/ml, preferably below 2000 ng/ml, and most preferably below 1000 ng/ml. The composition allows milnacipran to be delivered over approximately 24 hours, when administered to a patient in need, resulting in diminished incidence or decreased intensity of common milnacipran side effects such as sleep disturbance, nausea, vomiting, headache, tremulousness, anxiety, panic attacks, palpitations, urinary retention, orthostatic hypotension, diaphoresis, chest pain, rash, weight gain, back pain, constipation, vertigo, increased sweating, agitation, hot flushes, tremors, fatigue, somnolence, dyspepsia, dysoria, nervousness, dry mouth, abdominal pain, irritability, and insomnia.
**INTERNATIONAL SEARCH REPORT**

**CLASSIFICATION OF SUBJECT MATTER**

<table>
<thead>
<tr>
<th>IPC(7)</th>
<th>A61K 9/20, 9/22</th>
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<tbody>
<tr>
<td>US CL</td>
<td>424/464, 468</td>
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</tbody>
</table>

According to International Patent Classification (IPC) or to both national classification and IPC.

**FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

| U.S.     | 424/464, 468 |

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 practicable, search terms used)

Please See Continuation Sheet.

**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>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>US 6,066,643 A (PERRY) 23 May 2000 (23.05.2000), see entire document.</td>
<td>1-23</td>
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<tr>
<td>Y</td>
<td>US 5,958,429 A (WONG) 28 September 1999 (28.09.1999), see entire document.</td>
<td>1-23</td>
</tr>
</tbody>
</table>

**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 application or patent 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: 22 March 2004 (22.03.2004)

Date of mailing of the international search report: 27 May 2004

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703)305-3230

Authorized officer: Hameer N. Gajjar
Telephone No. (571) 272-0604

Form PCT/ISA/210 (second sheet) (July 1998)
INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(c) for the following reasons:

1. □ Claim Nos.:  
   because they relate to subject matter not required to be searched by this Authority, namely:

2. □ Claim 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:

3. □ Claim Nos.: 24  
   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.

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)
Continuation of B. FIELDS SEARCHED Item 3:
WEST
milnacipran, norepinephrine, delayed or sustained release, oral