Title: DOSING REGIMENS FOR SUBCUTANEously INFUSIBLE ACIDIC COMPOSITIONS

Abstract: The invention features methods, compositions, dosing regimens, and infusion pumps for subcutaneously infusing acidic solutions of L-DOPA prodrugs, such as esters and amides of L-DOPA, for the treatment of Parkinson's disease. The methods and acidic compositions of the invention can reduce the severity and rate of occurrence of transient local swelling, erythema, and persistent subcutaneous granulomas associated with subcutaneous delivery of certain agents used in the treatment of Parkinson's disease.
INTERNATIONAL SEARCH REPORT

International application No. PCT/US 13/44049

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 9/08, 31/195, 31/198, 31/215, 31/216; A61P 25/00, 25/16 (2013.01)

USPC - 514/538, 567, 649, 654; 560/43, 45; 562/433, 445

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(8) - A61K 9/08, 31/195, 31/198, 31/215, 31/216; A61P 25/00, 25/16 (2013.01)

USPC - 514/538, 567, 649, 654; 560/43, 45; 562/433, 445

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)


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>
</thead>
<tbody>
<tr>
<td>X</td>
<td>US 5,607,969 A (MILMAN, I et al.) May 4, 1997; column 3, lines 5-10, 12-16, 35-38, 42-50; column 6, lines 38-63; column 7, lines 1-13; column 11, lines 2-4, 10-12</td>
<td>1-2, 3/1-2, 4/1-2, 133, 216, 222-224</td>
</tr>
<tr>
<td>Y</td>
<td>WO 2005/023185 A2 (REMENAR, J et al.) March 17, 2005; page 18, paragraph 1, sentence 2; page 19, paragraph 1, sentence 2; page 20, paragraph 4, sentence 2</td>
<td>128, 217</td>
</tr>
<tr>
<td>A</td>
<td>WO 2003041646 A2 (FRENKEL, A et al.) May 22, 2003; page 3, lines 6-9</td>
<td>220</td>
</tr>
<tr>
<td>Y</td>
<td>3478 - Dopa. The Merck Index. Twelfth Edition. Published by Merck and Co., Inc., 1996; page 578</td>
<td>1-2, 3/1-2, 4/1-2, 133, 216, 228, 217, 221-224</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

Date of the actual completion of the international search 17 December 2013 (17.12.2013)

Date of mailing of the international search report 02 JAN 2014

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. 571-273-3201

Authorized officer: Shane Thomas

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774
## INTERNATIONAL SEARCH REPORT

### Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 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:

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:

   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.
- Group I: Claims 1-4, 128, 133, and 216-224 are directed toward a pharmaceutical composition for treating Parkinson's disease.
- Group II: Claims 129-132 and 139 are directed toward another pharmaceutical composition.
- Group III: Claims 134-137 are directed toward a subcutaneously infused aqueous pharmaceutical composition.
- Group IV: Claims 142-150 are directed toward a method for treating Parkinson's disease in a subject.

- Group V: Claims 151-161 and 201-215 are directed toward another method for treating Parkinson's disease in a subject.

- Continuation of the Next Supplemental Box:

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 additional fees, this Authority did not invite payment of additional fees.

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, 128, 133, and 216-224

### Remark on Protest

□ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

□ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

□ No protest accompanied the payment of additional search fees.

Form PCT/ISA/2 10 (continuation of first sheet (2)) (July 2009)
The inventions listed as Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I include a pharmaceutical composition comprising (i) greater than 0.05 M carbidopa prodrug salt or benzerazide salt, which is not present in Groups II-V; the special technical features of Group II include a pharmaceutical composition, wherein said pharmaceutical composition remains substantially free of LD precipitate for at least 24 hours when stored at about 37 degrees C; a kit comprising: (i) a first container comprising a sterile aqueous solution; (ii) a second container comprising a sterile, dry, reconstitutable solid; and (iii) instructions for combining the contents of the first container with the contents of the second container to form a pharmaceutical composition suitable for subcutaneous infusion into a subject for infusing said pharmaceutical composition into a subject for the treatment of Parkinson's disease and wherein said solid fully dissolves in said solution in less than 5 minutes at 25 degrees C; and wherein less than 10 percent of the LDEE is hydrolyzed when said first container and said second container are stored at 5 +/- 3 degrees C for a period of 3 months and for a period of 6 months, which are not present in Groups I and II-V; the special technical features of Group III include a subcutaneously infused aqueous pharmaceutical composition; i.e., infused at a rate greater than 0.01 mL per hour per infused site; and is, with fewer than 1/10th of the infused sites inflamed, swollen or hard 24 hours or more after the infusion, which are not present in Groups II and IV-V; the special technical features of Group IV include a method for treating Parkinson's disease in a subject, said method comprising delivering LD, or a prodrug of LD, via a second route of administration other than subcutaneous infusion, wherein (a) 50-500 mg of LD, or a prodrug of LD, is administered to the patient via said second route of administration within one hour before or after initiating an infusion of the LD prodrug pharmaceutical composition; or administration at three or more times during the day, each dose being separated from a previous dose by at least 2 hours; and the total dose of LD, or a prodrug of LD, administered to the patient via said second route of administration during a 24 hour period is less than three times the molar dose of the infused LD prodrug acid addition salt during said 24 hour period; or (b) a circulating plasma LD concentration less than 5,000 ng/ml is continuously maintained for a period of at least 8 hours during said infusion, which are not present in Groups III and V; the special technical features of Group V include a method for treating Parkinson's disease in a subject, said method comprising subcutaneously infusing into the subject a LD prodrug solution in a pulsing dosing regimen, wherein said pulsing dosing regimen comprises (i) a delivery period during which said LD prodrug solution is infused at a first site for from 1 second to 3 hours; and (ii) following step (i), a non-delivery period during which said LD prodrug solution is administered at a substantially reduced rate at said first site for from 10 to 120 minutes; (iii) a delivery period during which said LD prodrug solution is infused at a second site for from 1 second to 3 hours; and (iv) following step (iii), a non-delivery period during which said LD prodrug solution is infused at a substantially reduced rate at said second site for from 10 to 120 minutes, and optionally repeating steps (i), (ii), (iii), and (iv); and utilizing the method with an ambulatory infusion pump system comprising (i) a drug reservoir comprising a LD prodrug solution; (ii) a first cannula in fluid communication with the drug reservoir; and (iii) a software unit comprising a program for controlled infusion of said LD prodrug solution in a pulsing dosing regimen, which are not present in Groups I-V.

The common technical features of Groups I-V are a pharmaceutical composition comprising an aqueous solution containing from 0.15 to 1.6 M LD prodrug acid addition salt, including LDEE, LDME, or a salt thereof, and having a pH of from 2.1 to 3.9, wherein said pharmaceutical composition is subcutaneously infusible, and a method for treating Parkinson's disease in a subject.

These common technical features are disclosed by US 5,525,631 A to Milman, et al. (hereinafter 'Milman'). Milman discloses a pharmaceutical composition comprising an aqueous solution (pharmaceutical compound in an aqueous solution; claims 1, 5) containing from 0.15 to 1.6 M LD prodrug acid addition salt (L-DOPA ethyl ester, present as a free base in an acid solution, where the therapeutically effective concentration of L-DOPA ethyl ester is between about 10 and about 1,000 mg equivalent of L-DOPA per milliliter (0.05 M to 5.07 M); claims 1, 3, 6, 10), including LDEE (L-DOPA ethyl ester is LDEE; claim 1), LDME, or a salt thereof, and having a pH of from 2.1 to 3.9 (composition preferably has a pH between about 1.5 and about 5.5; claim 9), wherein said pharmaceutical composition is subcutaneously infusible (L-DOPA ethyl ester composition of this invention may be formulated for subcutaneous administration; column 4, lines 12-19; column 8, lines 60-65, example 12), and a method for treating Parkinson's disease in a subject (a method of treating a patient suffering from Parkinson's disease; abstract).

Since the common technical features are previously disclosed by Milman, these common features are not special and so Groups I-V lack unity.