

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2019/049340

International filing date (day/month/year)
03.09.2019

Priority date (day/month/year)
04.09.2018

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/444 A61P25/06

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 14-24

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 14-24 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13~~ter~~.1(a) or (b).

☒ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-13</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-13</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-13</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Documents

- D1 Peter J Goadsby ET AL: "Migraine - Current understanding and Treatment",
N Engl. J. Med,
vol. 346, no. 4, 24 January 2002 (2002-01-24), pages 257-270,
XP055542054,
DOI: 10.1056/NEJMra010917
- D2 Markus Färkkilä ET AL: "Efficacy and tolerability of lasmiditan, an oral 5-HT_{1F} receptor agonist, for the acute treatment of migraine: a phase 2 randomised, placebo-controlled, parallel-group, dose-ranging study",
LANCET NEUROLOGY,
vol. 11, no. 5, 1 May 2012 (2012-05-01), pages 405-413, XP055521638,
GB
ISSN: 1474-4422, DOI: 10.1016/S1474-4422(12)70047-9
- D3 Anonymous: "Dose-ranging Study of Oral COL-144 in Acute Migraine Treatment",
ClinicalTrials.gov, 10 September 2009 (2009-09-10), XP055508622,
Retrieved from the Internet:
URL:<https://web.archive.org/web/20090910220814/clinicaltrials.gov/ct2/show/NCT00883051>
[retrieved on 2018-09-20]
- D4 JESSICA C OSWALD ET AL: "Lasmiditan for the treatment of acute migraine: a review and potential role in clinical practice",
JOURNAL OF PAIN RESEARCH,
vol. Volume 11, 8 October 2018 (2018-10-08), pages 2221-2227,
XP55640840,
GB
ISSN: 1178-7090, DOI: 10.2147/JPR.S152216
- 1 D1 (the whole document; table 3) reviews current understanding and treatment of migraine. It discloses chronic nightly administration of amitriptyline to prevent migraine.
- 2 D2 and D3 disclose the use of lasmiditan (2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide) for treatment of migraines and dosage ranging studies.
- 3 D4 is a further review on the use of lasmiditan for treatment of migraines, which is published after the priority date.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

- 4 The present application contains 24 claims, of which at least 6 are independent method claims. There is no clear distinction between the independent claims because of overlapping scope. There are so many claims, and they are drafted in such a way that the claims as a whole are not in compliance with the provisions of clarity and conciseness of Art. 6, as it is particularly burdensome for a skilled person to establish the subject-matter for which protection is sought. For this reason, the analysis under Item V is limited to claims 1-13.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Independent claims

- 5 The following independent claims are considered: 1 (method).

Art. 33(2)

- 6 The claims are novel in that the prior art does not disclose chronic nightly use of lasmiditan in the prevention of migraine in a patient. D1 does not concern lasmiditan. D2-D4 relates to lasmiditan but not to chronic nightly use thereof.

Art. 33(3)

Closest prior art

- 7 D1 is the closest prior art, since it discloses chronic nightly administration of amitriptyline to prevent migraine (i.e. same purpose with a similar dosage regimen).

Distinguishing features

- 8 The replacement of amitriptyline with lasmiditan.

Technical effect

- 9 No comparative data.

Problem

- 10 The provision of a further medical treatment for prevention of migraines.

Solution

- 11 The subject-matter of claim 1 via the aforementioned distinguishing features.

Obviousness

- 12 None of the prior art suggests chronic nightly administration of lasmiditan. D2-D4 are mainly concerned with acute treatment of migraine of lasmiditan, not prevention thereof, let alone via chronic nightly administration. Common general knowledge alone is also not helpful given the specific nature of the solution. Thus, the claims are inventive.

Art. 33(4)

- 13 The subject-matter of the claims is industrially applicable in the field of treatment of migraine.

R. 67.1(iv)

- 14 The claims cover methods of treatment by therapy. Certain designated Offices such as the EPO do not regard such matter as patentable.

Re Item VIII

Certain observations on the international application

Art. 5, 6

- 15 The most serious deficiency is insufficiency of disclosure. For a medical use claim, the application must demonstrate the suitability of the composition for the medical application. Furthermore, the claimed effect, namely prevention of migraine, must be plausible over the whole claimed scope. Here, the claims merely relate to "chronic nightly use". This is firstly an unclear relative term - there is no room for discretion concerning the clarity of essential features. Secondly, from considering the dependent claims, chronic nightly use could encompass a treatment span of less than five days, which is very short. Also no dosage regimen is specified. On the contrary, the examples focus on very long treatment spans (e.g. 3 months or more) at specific dosages that are reasonably high (e.g. at least 100 mg dose). The skilled person would not regard a very long treatment at a specific dose to be comparable to very short treatment at an undefined, and potentially insignificant, dose. Thus, the claimed subject-matter is both unclear, and insufficiently disclosed over the whole claimed scope. Suggestion: limit the claims to a specific minimal treatment span of a reasonable length (e.g. at least 30 days) and to a specific dose range (e.g. 50-200 mg) that is a fair generalisation of the doses used in the examples. Of course, there should be a directly and unambiguously derivable basis for all amendments in the application as filed, particularly regarding endpoints of ranges.

- 16 Claims 14 onwards should be deleted due to lack of conciseness (see Item III).