

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 20170413	FOR FURTHER ACTION	See item 4 below
International application No. PCT/EP2017/060780	International filing date (<i>day/month/year</i>) 05 May 2017 (05.05.2017)	Priority date (<i>day/month/year</i>) 06 May 2016 (06.05.2016)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant ESTEVE PHARMACEUTICALS, S.A.		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).																								
2.	This REPORT consists of a total of 6 sheets, including this cover sheet.																								
In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																									
3.	This report contains indications relating to the following items: <table style="width: 100%;"> <tr> <td style="width: 5%; text-align: center;">☒</td> <td style="width: 25%;">Box No. I</td> <td style="width: 70%;">Basis of the report</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;">☒</td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;">☒</td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	☒	Box No. I	Basis of the report	☐	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 Article 35(2) with regard to novelty, inventive step or 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
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4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).																								

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Date of issuance of this report 06 November 2018 (06.11.2018) Authorized officer Nora Lindner e-mail: pct.team5@wipo.int
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
see form PCT/ISA/220

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/EP2017/060780

International filing date (day/month/year)
05.05.2017

Priority date (day/month/year)
06.05.2016

International Patent Classification (IPC) or both national classification and IPC
INV. C07D471/04 C07D487/04 C07D498/10 A61K31/551 A61P29/00 A61P25/00

Applicant
LABORATORIOS DEL DR ESTEVE, S A

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. 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>1-17</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-17</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-17</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

Item V.

Reference is made to the following document:

D1: EP 2 163 554

1. Novelty

Prior art document D1 discloses pyrimidodiazepinone derivatives that differ from the compounds of general formula (I) of current claim 1 through the presence of a third fused ring (whereas the diazepine substituent R₁ of the present application cannot form a fused ring with said diazepine).

No compounds of general formula (I) according to current claim 1 could be retrieved from the available prior art.

The present application appears to be novel in the sense of Article 33(2) PCT.

2. Inventive Step

Document D1, which can be regarded as the closest prior art to the present application, discloses pyrimidodiazepinone compounds having an affinity towards the $\alpha 2\delta$ subunit of VGCC useful for the treatment of pain. As previously mentioned, the present application differs from D1 through the substitution pattern of the pyrimidodiazepinone ring system.

Thus, the problem to be solved by the present application can be regarded in the provision of alternative pyrimidodiazepinone compounds useful for the treatment of pain.

The data provided in Table 1 of the present application seem to indicate that at least some of the compounds according to general formula (I) of current claim 1 actually solve the aforementioned technical problem. In addition, nothing in the art would have prompted the person skilled in the art to modify the pyrimidodiazepinone compounds of formula (I) of claim 1 of D1 in such a way to arrive at the compounds of formula (I) of claim 1 of the present application.

The present application seems to fulfil the requirements of Article Article 33(3) PCT.

Item VIII.

The present application does not meet the requirements of clarity and conciseness set down Article 6 PCT for the following reasons:

- the term "isomer" does not limit the compounds of formula (I) of current claim 1 to their stereoisomers, it also includes the constitutional isomers, i.e. the compounds that have the same molecular formula as the compounds of current claim 1 but in which the atoms are joined together in a different way. It is therefore unclear which compounds are actually covered by such a definition. Support within the meaning of Articles 5 and 6 PCT is to be found only for the compounds of structural formula (I) while other constitutional isomers are simply not supported by the description. This remark also applies to current claim 17,

- claim 1 encompasses an undetermined number of compounds that are defined only by reference to a desired functional activity, namely the compounds being "prodrugs". This functional term does not give a specific technical guidance for the ascertainment of the scope of the claim as to which chemical entities are suitable "prodrugs" having the desired function without imposing an unreasonable burden: in order to know which compounds are prodrugs and which are not, the skilled person would have to carry out *in vivo* tests. This remark also applies to current claim 17,

- the term "preferably" is meaningless in the wording of a claim. Therefore current claims 2-5, 7 and 9 are not concise. The preferred embodiments disclosed after the term "preferably" should be either deleted or made the subject of a further dependent claim. Alternatively, the claims could be limited to the preferred embodiments only. A similar remark also applies to the term "especially" in current claims 15 and 16,

- the fourth heterocycle R_3 depicted in current claim 5 contains a group R, the definition of which is not provided in the claims. Current claim 5 is therefore unclear,

- current claim 15 refers to "a disease mediated by the subunit $\alpha 2\delta$ ". There is, however, no universal and exhaustive list of which diseases fall within said functional definition of the pathology. This has the effect that the person skilled in the art cannot decide clearly the scope of current claim 15. This objection could be overcome by introducing in the claims a list of pathological conditions (diseases) cited in the application (which is in fact already the case in current claim 16)

The skilled person would understand the term alkyl and its combination with other chemical moieties as fully saturated (i.e. a radical of formula $-C_nH_{2n+1}$). However, in the present application, cycloalkyl and heterocycloalkyl can include unsaturations too. In order to avoid a lack of clarity of the claims (e.g. in current claim 6, wherein R_3 can be tetrahydropyridine vs. claim 1, on which claim 6 depends, wherein R_3 can be heterocycloalkyl), the specific definitions should be introduced in claim 1.