

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/US2018/041378

International filing date (day/month/year)
10.07.2018

Priority date (day/month/year)
17.07.2017

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/24 A61K31/00

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

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

2. Citations and explanations

see separate sheet

Re Item V

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

1 Reference is made to the following documents:

- D1 EP 3 025 708 A1 (CJ HEALTHCARE CORP [KR]) 1 June 2016
(2016-06-01)
- D2 Nisharani Nisharani Ranpise ET AL: "Formulation and Development of Fixed Dose Combination of Antihypertensive and Antidiabetic Agent for treatment of Co-existent Type Two Diabetes Mellitus and Hypertension", Indian Journal of Pharmaceutical Education and Research, vol. 48, no. supplementary, 1 December 2014 (2014-12-01), pages 10-117, XP055502436, IN
ISSN: 0019-5464, DOI: 10.5530/ijper.48.4s.14

2 **Novelty**

The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-17 is new in the sense of Article 33(2) PCT.

3 **Inventive step**

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-17 does not involve an inventive step in the sense of Article 33(3) PCT.

3.1 For claim 1

3.1.1 Document D1 can be considered as the closest prior art. D1 teaches the use of a bi-layer tablet composition comprising (a) a sustained release layer comprising metformin and (b) an immediate release layer comprising an HMG Co-A reductase inhibitor atorvastatin for the treatment of coexistent type two

diabetis mellitus (TTDM) and cardiovascular complications, wherein the tablet composition has improved stability (page 1, [0001]; page 4, [0023]; pages 8-9, example 1).

Claim 1 differs from D1 in that (i) the tablet composition further comprises an immediate release composition comprising the ARB valsartan and (ii) the HMG Co-A reductase inhibitor atorvastatin is present in the tablet composition in the outer coating layer. The technical effect provided by these differences is the improvement of patient compliance in the treatment of coexistent TTDM, hypertension and cardiovascular complications by providing a fixed dose composition and the better stability of the composition due to the absence of interaction between valsartan and atorvastatin. However, the search division is of the opinion that the stability problem derived from the incompatibility between valsartan and atorvastatin has not been credibly demonstrated by the application for the following reasons:

- The application mentions that by separating the atorvastatin from valsartan improves the stability of the composition. As support for this assumption, the application presents technical data that compares a layered tablet composition according to claim 1 with a tablet composition wherein atorvastatin and valsartan are present in the same blend (page 20, lines 15-20, table C). However, from this technical data it is not possible to ascertain if the higher amount atorvastatin lactone impurity is related to a drug-drug incompatibility issue or to a drug-excipient(s) incompatibility issue. The search division notes that not all the excipients used in the atorvastatin/valsartan blend are mentioned in the application (page 19, lines 11-18).

- 3.1.2 Accordingly, the search division holds that the technical problem is to provide an alternative solid pharmaceutical composition with improved patience compliance.
- 3.1.3 In addition to D1, D2 teaches that the use of fixed dose combination (FDC) improves the patience compliance of coexistent TTDM, hypertension and cardiovascular complications (page 110, left column, lines 30-49; page 110, right column, [0002], lines 1-2, 10-17; page 110, right column, [0003], lines

1-6). One of the fixed dose compositions taught in D2 comprises a bilayer tablet composition comprising the combination of metformin, atorvastatin and telmisartan (page 112, table 1).

Although the particular structure of the tablet composition of claim 1 is not taught in the above prior art, it is nevertheless merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.

Therefore, no inventive step is present in the subject-matter of claim 1 (Article 33(3) PCT).

3.2 The same reasoning applies, *mutatis mutandis*, to the subject-matter of the independent claims 15-16, which therefore is also considered not inventive.

3.3 The dependent claims 2-14 and 17 do not contain any features which, in combination with the features of claim 1 to which they refer, meet the requirements of the PCT in respect inventive step because they relate only to minor modifications obvious for the skilled person (see documents D1-D2 and the corresponding passages cited in the search report) (Article 33 (3) PCT).

4 Industrial Applicability

Claims 1-17 are considered to be industrially applicable in the sense of Article 33(4) PCT.