PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2019/037146	14.06.2019	22.06.2018

International Patent Classification (IPC) or both national classification and IPC
INV. A61K47/02 A61K47/10 A61K38/00 A61K38/16 A61P3/10

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 43*bis*.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 notifed the International Bureau under Rule 66.1*bis*(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:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of this opinion
see form PCT/ISA/210

Authorized Officer
Wörth, Christian
Telephone No. +49 89 2399-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2019/037146

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 43*bis*.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 13*ter*.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 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.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 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-43
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-43
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-43
	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 Prior art

Reference is made to the following documents:

D1 US 9 474 780 B2 (LILLY CO ELI [US]) 25 October 2016 (2016-10-25)

D2 US 2012/329708 A1 (DIMARCHI RICHARD D [US] ET AL) 27 December 2012 (2012-12-27)

2 Subject-matter of the application

The present application contains 5 independent claims relating to

- a pharmaceutical composition comprising tirzepatide (claim 1)

- a method of treating diabetes comprising administering said composition (claim 36)

- a method of treating obesity comprising administering said composition (claim 39)

- said composition for use in the treatment of diabetes (claim 42)

- said composition for use in the treatment of obesity (claim 43).

3 Patentability

3.1 The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

3.2 Patentability, in particular novelty and inventive step, of claims 36-41 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

4 Novelty (Art. 33(2) PCT)

4.1 Document D1 discloses in claim 16 a pharmaceutical composition comprising tirzepatide. In claim 17 as well as in col. 5, lines 32-66, methods of treating diabetes and obesity comprising administering a pharmaceutical composition comprising tirzepatide are disclosed.

D1 does not disclose compositions comprising dibasic sodium phosphate.

4.2 Dockument D2 discloses in claim 24 a pharmaceutical composition comprising a different GIP/GLP-1 co-agonist peptide. in [0250]-[0262], pharmaceutical compositions are disclosed.

D2 does not disclose compositions comprising tirzepatide.

4.3 ***The requirements of Art. 33(2) PCT are presently deemed met.***

5 Inventive step (Art. 33(3) PCT)

5.1 The present application seeks to provide tizepatide compositions with acceptable stability and patient injection site experience (see page 2, lines 14-17).

D1 generally describes compositions containing a GIP/GLP1 agonist, administered by parenteral routes describes and claims tirzepatide. Hence D1 is considered as closest prior art.

The presently claimed subject-matter differs from D1 in view of the presence of either

- NaCl and dibasic sodium phosphate or

- propylene glycol and dibasic sodium phosphate.

5.2 The effect of this difference appears to reside in compositions with increased shelf life (table 4) and reduced pain at the site of injection (table 8).

5.3 Hence the problem to be solved can be seen as the provision of tizepatide compositions with acceptable stability and patient injection site experience.

5.4 The solution consists in compositions according to claim 1.

5.5 The problem is considered as solved in view of tables 4 and 8.

5.6 The solution is considered to involve an inventive step for the following:

5.6.1 D1 as closest prior art does not pont towards compositions comprising aCl and dibasic sodium phosphate or propylene glycol and dibasic sodium phosphate.

5.6.2 D2 discloses in [0250]-[0262] compositions comprising a GIP/GLP-1 co-agonist peptide. Sodium chloride, propylene glycol and dibasic sodium phosphate are mentioned among a list of possible suitable excipients. However, D2 does not contain a pointer to reduced pain at site of application or improved shelf life.

5.7 ***Hence the claimed subject-matter is deemed to meet the requirements of Art. 33(3) PCT.***