

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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/EP2018/072835

International filing date (day/month/year)
24.08.2018

Priority date (day/month/year)
24.08.2017

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/00 A61K38/00 A61K47/10

Applicant
NOVO NORDISK A/S

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:



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

Schüle, Stefanie

Telephone No. +49 89 2399-0



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>1-15</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-15</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-15</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 DOCUMENTS

Reference is made to the following documents:

- D1 WO 2014/060472
- D2 WO 2006/097537
- D3 Basf: "BASF Chemical Emergency Medical Guidelines", 1 January 2016, Retrieved from the Internet:
URL:https://www.basf.com/documents/corp/en/sustainability/employees-and-society/employees/occupational-medicine/medical-guidelines/Phenol_B_BASF_medGuidelines_E014.pdf

2 NOVELTY (Art. 33(2) PCT)

- 2.1 The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-15 is new in the sense of Article 33(2) PCT.
- 2.2 The examiner agrees with the applicant that none of the cited documents discloses a composition which is free of phenol and is suitable for parenteral administration, is an aqueous solution comprising at least 60 %w/w water, or further comprises one or more pharmaceutically acceptable excipients selected from the group consisting of a buffer or an isotonic agent.

3 INVENTIVE STEP (Art. 33(3) PCT)

- 3.1 The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-15 involves an inventive step in the sense of Article 33(3) PCT.
- 3.2 Document D2 is considered to represent the closest prior art and discloses an aqueous composition comprising semaglutide and phenol. The subject-matter of claim 1 differs from D2 in that not more than 0.01 % phenol is contained.

- 3.3 The applicant pointed out that the difference resulted in a marked improvement of stability of semaglutide.
- 3.4 Compositions comprising semaglutide, propylene glycol, and disodiumhydrogenphosphate dihydrate and optionally phenol at a pH of 7.4 were prepared in the examples of the application. Compositions comprising 1 mg/ml and one comprising 1.34mg/ml semaglutide were tested for their chemical stability over 3 months (Tables 1 and 2). The physical stability of compositions comprising 0.5, 1.0, and 2 mg/ml was also tested (Table 3). Similar compositions were prepared with liraglutide as reference.
- 3.5 It can be concluded from example 3 that the presence of propylene glycol does not seem to influence the stability, the same applies to the use of citrate instead of propylene glycol. Thus, it appears that the improved stability results in fact from the absence of phenol.
- 3.6 Therefore the problem is formulated as provision of an improved liquid composition comprising semaglutide.
- 3.7 The solution according to claim 1 is considered as involving an inventive step, because the omission of phenol leads to an increase in stability which was not foreseeable in particular in view of example 2 of the application wherein the omission of phenol leads to a decrease in stability in compositions comprising liraglutide..

4 INDUSTRIAL APPLICABILITY (Art. 33(4) PCT)

The subject-matter of claims 1-15 is industrial applicable according to Art. 33(4) PCT.