

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/EP2019/079214

International filing date (day/month/year)
25.10.2019

Priority date (day/month/year)
26.10.2018

International Patent Classification (IPC) or both national classification and IPC
INV. A61K38/26 A61K9/00 A61K47/18 A61P3/10

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:



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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>1-15</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 Reference is made to the following documents:

D1 WO 2017/186896 A1

D2 WO 2018/115901 A1

D3 WO 2016/038521 A1

D4 WO 2005/049061 A2

2 None of the cited documents discloses a liquid composition comprising semaglutide, an isotonic agent and histidine in a concentration of 0.5-100 mM, wherein the pH of the composition is in the range of 6-10.

Therefore, the subject-matter of claims 1-15 is novel pursuant to Art. 33(2) PCT.

3 The subject-matter of present claims 1-15 is considered to involve an inventive step in the sense of Art. 33(3) PCT for the following reasons.

D1 is considered to represent the closest prior art and discloses an aqueous composition comprising semaglutide, a buffer being disodium phosphate dihydrate, an isotonic agent being propylene glycol and phenol at a pH of 7.4.

The subject-matter of claim 1 differs from D1 in that the composition additionally contains histidine.

The present application shows the preparation of aqueous solutions comprising semaglutide, propylene glycol, and disodium hydrogen phosphate dihydrate and histidine at a pH of 7.4. It is shown that the presence of histidine in the formulations results in less formation of high molecular weight proteins (HMWPs), as well as lower formation of 2 hydrophobic impurities as compared to the same formulation without histidine.

Therefore the problem can be formulated as the provision of an improved liquid composition comprising semaglutide with better chemical stability.

The solution proposed is the addition of histidine in a concentration of 0.5-100 mM.

Histidine is listed as a possible buffer or stabilizer in peptide formulations (see D3, D4). However, it is considered that the skilled man did not have any hint to add it to the known formulation of semaglutide of D1 with the expectation of

increasing stability. Furthermore, D2 (see example 1) states that the addition of histidine to a formulation with a similar GLP-1 agonist (liraglutide) was observed to impair the stability of said peptide, so that the skilled man would be rather discouraged to add histidine.

In view of the examples, it can be concluded that the presence of histidine leads to an improved chemical stability of the formulations.

Claims 2-15 are dependent or encompass a composition according to claim 1 and as such also meet the requirements of the PCT with respect to novelty and inventive step.