PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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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/GB2019/053440	05.12.2019	05.12.2018

International Patent Classification (IPC) or both national classification and IPC
INV. A61K38/48 A61P25/00

Applicant
IPSEN BIOPHARM LIMITED

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:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Dolce, Luca Telephone No. +49 89 2399-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2019/053440

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	3-22
	No:	Claims	1, 2
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-22
	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 VIII

1 CLARITY, CONCISENESS, SUPPORT

1.1 The present application discloses a study carried out in mice models for traumatic brain injury (TBI), in which the activity of botulinum neurotoxin (BoNT, and particularly the commercially available Dysport, i. e. abobotulinumtoxin A) in treating *allodynia* (a condition related to pain-perception) is evaluated.

Examples 1-4 show that when BoNT was injected subcutaneously at the site the injury suture, at different time-points post injury, treated mice showed improvement in TBI-induced allodynia overtime.

Note: examples 5-8 are only prophetic.

1.2 Claims 1, 2 are unjustifiably broad in light of the actual disclosure of the application and should be redrafted by limiting them to the content of the experimental section (see above). The claims also lack support for all the conditions, modes of administration etc which are not shown in the application and for which there is a reasonable doubt of plausibility (e. g. those indicated in the dependent claims).

1.3 Claims 1-22 often contain unclear terms, such as "*about* 30 units, "*about* 2 hours", "based in part" etc. Claim 9 is redundant with claim 3. Step (d) of claim 17 is unclear in that no percentage of identity can be estimated in the absence of specific amino acid sequences.

Item V

For the assessment of the present claims 1, and 3-22 (in part), referring to methods of treatment, on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first and further use in medical treatment.

2 NOVELTY

2.1 The use of BoNT for treating symptoms of TBI is well known in nature, in muscle-associated conditions (e. g. spasticity) as well as in neuropathic pain syndromes and in general in pain management (due the potential activity of the toxin in suppressing the release of nociceptive and inflammatory mediators in the body).

D1 discloses the use of BoNT for treating postcraniotomy headache after TBI, by injection at peri-incisional sites (see e.g. discussion, pag. 787).

D5 discloses similar subject-matter, wherein BoNT is used to treat post-traumatic headaches (see pages. 592-593).

2.2 Documents D1, D5 are novelty destroying for claims 1 and 2.

2.3 Claims 1, 2 are not novel.

3 INVENTIVE STEP

3.1 Dependent claims 3-22 are either not novel in light of the prior art or they do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step because they refer to routine modifications and standard laboratory practice.

3.2 Further to D1 and D5, the Applicant's attention is drawn to the following documents: D2, is a review about BoNT for use in treating pain (see pages 2-3), D3 discloses the use of of BoNT for treating central neuropathic pain (see e. g. pages 3-5). D4 discloses the use of BoNT to treat headache and allodynia (see e. g. pages 1 and 6).

Any of D2-D4 can be used alone, in alternative to D1 or D5, as the closest prior art. The skilled person starting from any of these documents would reach the subject-matter of claims 1-22 by applying routine modifications and standard laboratory practice.

3.3 Claims 1-22 are not inventive.

CITATIONS

D1 HEATHER M. MACKENZIE ET AL: "Peri-Incisional Botulinum Toxin for Chronic Postcraniotomy Headache After Traumatic Brain Injury: A Case Series", PM&R, vol. 7, no. 7, 1 July 2015 (2015-07-01), pages 785-788, XP055542506, AMSTERDAM, NL ISSN: 1934-1482, DOI: 10.1016/j.pmrj.2015.02.015

D2 SHILPADEVI PATIL ET AL: "Botulinum Toxin: Pharmacology and Therapeutic Roles in Pain States", CURRENT PAIN AND HEADACHE REPORTS, vol. 20, no. 3, 15 February 2016 (2016-02-15), XP055542572, US ISSN: 1531-3433, DOI: 10.1007/s11916-016-0545-0

D3 JIHYE PARK ET AL: "Botulinum Toxin for Central Neuropathic Pain", TOXINS, vol. 10, no. 6, 1 June 2018 (2018-06-01), page 224, XP055542241, DOI: 10.3390/toxins10060224

D4 WO 2006/078588 A2 (ALLERGAN INC [US]; TURKEL CATHERINE C [US]; BRIN MITCHELL F [US]) 27 July 2006 (2006-07-27)

D5 LIPPERT M.: "Botulinum toxin in the treatment of post-traumatic headache - case study", NEUROLOGIA I NEUROCHIRURGIA POLSKA, vol. 46, no. 6, 1 January 2012 (2012-01-01), pages 591-594, XP055268207,PL ISSN: 0028-3843, DOI: 10.5114/ninp.2012.32109