

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/IB2022/059429	International filing date (day/month/year) 03.10.2022	Priority date (day/month/year) 04.10.2021
International Patent Classification (IPC) or both national classification and IPC INV. A61K31/519 A61K9/107 A61K9/19 A61K9/20 A61K47/42 A61K45/06 A61P43/00		
Applicant NEURIM PHARMACEUTICALS (1991) LTD.		

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 Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Benbow, Susanne Telephone No. +49 30 25901-0
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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 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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),
 - ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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>38-43, 51-53, 55, 56</u>
	No: Claims	<u>1-37, 44-50, 54</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-56</u>
Industrial applicability (IA)	Yes: Claims	<u>1-56</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

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 US 2019/117577 A1 (AL HUSBAN FARHAN ABDEL KARIM MOHAMMAD [GB] ET AL) 25 April 2019 (2019-04-25)
- D2 CN 105 943 515 A (SHANDONG LUKANG PHARMACEUTICAL CO LTD) 21 September 2016 (2016-09-21)
- D3 CN 105 669 674 A (CHONGQING SHENGHUAXI PHARMACEUTICAL CO LTD ET AL.) 15 June 2016 (2016-06-15)
- D4 KR 102 007 731 B1 (IAC IN NAT UNIV CHUNGNAM [KR]) 6 August 2019 (2019-08-06)
- D5 NA YOUNG-GUK ET AL: "Strategic approach to developing a self-microemulsifying drug delivery system to enhance antiplatelet activity and bioavailability of ticagrelor",
INTERNATIONAL JOURNAL OF NANOMEDICINE,
vol. Volume 14, 1 February 2019 (2019-02-01), pages 1193-1212,
XP093007293,
DOI: 10.2147/IJN.S190426
Retrieved from the Internet:
URL:<https://www.dovepress.com/getfile.php?fileID=48081>
- D6 US 10 614 684 B2 (THE US GOV AS REPRESENTED BY THE DEPARTMENT OF VETERANS AFFAIRS [US] E) 7 April 2020 (2020-04-07)

Unless otherwise indicated, reference is made to the relevant passages emphasized in the International Search Report.

2 The following remark applies to claims 37-56:

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 Article 6 PCT and Article 5 PCT

- 3.1 Claims 1-3, 44-50, 54 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

In this context, the above examination for said claims has been based on what the examiner considered the technical features referring to said claims, i.e., *prima facie*,

A solid orally disintegrating table (ODT) or a solid orally dissolving film (ODF) or a Self-microemulsifying drug delivery system (SMEDDS) comprising ticagrelor, an enantiomer thereof, or a pharmaceutically acceptable salt thereof and a second agent in a weight ratio of 1:0.1 to 1:50, and an excipient

for claims 1-3,

A method of treating a subject diagnosed with an autism spectrum disorder, an intellectual disability, epilepsy, an anxiety disorder, a mood disorder, a disorder of social interaction, irritability, aggression, self-injurious behavior, hyperactivity, inattention, Fragile X syndrome, or diagnosed with elevated TNF α , or diagnosed with elevated inflammatory cytokine marker of neuroinflammation comprising administering ticagrelor, an enantiomer thereof, or a pharmaceutically acceptable salt thereof to the subject or administering a combination of ticagrelor, an enantiomer thereof, or a pharmaceutically acceptable salt thereof with a second agent in a weight ratio of 1:0.1 to 1:50 to the subject

for claims 44-50, 54.

In addition, claims 2-3, 44-50, 54, attempt to define the pharmaceutical composition/dosage form in terms of *in vivo* absorption / bioavailability / pharmacokinetic parameters. In the present case, lack of clarity under Article 6 PCT arises from the uncertainty as to the study design / the testing conditions used for the determination of the parametric values thus rendering the definition of the pharmaceutical composition/dosage form by said values unclear; and lack of sufficient disclosure under Article 5 PCT arises because in the absence of any information about / sufficient guidance as to / which features give rise to the parametric values the invention cannot be carried out without undue experimentation.

- 3.2 Present claims 21-25, 29-31 relate to a product which is defined by its parameters, e.g. water absorption ratio, wetting time, tensile strength and so on, without indicating the measuring conditions. The use of these parameters in the present context is considered to lead to a lack of clarity under Article 6 PCT, because (i) the claims do not clearly identify the products encompassed by it, i.e. by mentioning in the claims the method of measurement used to determine said parameters; and (ii) the parameter cannot be clearly and reliably determined by indications in the description and/or by objective procedures usual in the art.
- 3.3 The term "derivative" in claim 35 renders its scope unclear, since it is not known to the skilled reader which structures are intended to be encompassed by this term. Terms like analogues/derivatives include an unlimited number of compounds obtainable from another compound by some undetermined chemical modification (including compounds which are structurally remote from the starting material), functional derivatives (such as compounds, wherein hetero atoms are exchanged by alternative atoms), compounds with numerous different types of side groups etc. There is, however, no clear definition to which extent the compounds according to claim 35 may be modified while still being regarded as "derivatives". This has the effect that the person skilled in the art cannot decide clearly which compounds are to be covered by the claims and which are not. Consequently, claim 35 does not fulfil the requirements of Article 6 PCT.
- 4 Article 33(1)(2) PCT
- The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of independent claims 1 and 37 is not new in the sense of Article 33(2) PCT.
- 4.1 The documents D1-D3 disclose:
- A solid orally disintegrating tablet (ODT) comprising ticagrelor, an enantiomer thereof, or a pharmaceutically acceptable salt thereof and a second agent in a weight ratio of 1:0.1 to 1:50, and an excipient.
- As the second agent e.g. F-MELT type M (D1), mannitol (D2), carboxymethyl starch sodium (D3) is regarded. Additional excipients are e.g. colloidal silica (D1), stearic acid (D2), magnesium stearate (D3).
- The documents D4-D5 disclose:

A Self-microemulsifying drug delivery system (SMEDDS) comprising ticagrelor, an enantiomer thereof, or a pharmaceutically acceptable salt thereof and a second agent in a weight ratio of 1:0.1 to 1:50, and an excipient.

As the second agent e.g. Transcutol P (D4, D5) is regarded. Additional excipients are e.g. Capmul MCM (D4, D5).

Therefore, D1-D5 anticipate the subject-matter of independent claim 1.

4.2 The document D6 discloses:

A method of treating a subject diagnosed with an autism spectrum disorder comprising administering ticagrelor, an enantiomer thereof, or a pharmaceutically acceptable salt thereof to the subject.

Therefore, D6 anticipates the subject-matter of independent claim 37.

5 Article 33(1)(3) PCT

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-56 does not involve an inventive step in the sense of Article 33(3) PCT.

5.1 Being not new, the subject-matter of independent claims 1 and 37 cannot be considered as involving an inventive step.

5.2 The dependent claims do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to novelty and/or inventive step. The features claimed in these dependent claims represent matters of common practice to a skilled person; as such, they represent mere known alternative embodiments to the compositions / therapy in question. In the absence of any indication as to a (further) technical effect being obtained by these features, the claims concerned lack an inventive step.

It is emphasized that solid orally dissolving films (ODF) are very well known in the art; therefore, a person skilled in the art would prepare as an alternative to an ODT disclosed in any of D1-D3 an ODF comprising ticagrelor as a matter of common practice based on routine experiments. Thus, this obvious alternative defined in claim 1 is not considered to be inventive.

6 Claims 1-56 of the present application appear to meet the requirements of Article 33(4) PCT regarding industrial applicability.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date (day/month/ year)	Filing date (day/month/ year)	Priority date (valid claim) (day/month/year)
WO 2021/242970 A1	02/12/2021	27/05/2021	29/05/2020

This document discloses an oral SMEDDS comprising ticagrelor and another drug, namely DIM (3,3'-diindolylmethane).