

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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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/EP2019/060220	International filing date (day/month/year) 19.04.2019	Priority date (day/month/year) 19.04.2018
International Patent Classification (IPC) or both national classification and IPC INV. A61K31/565 A61K31/55 A61K31/57 A61K31/585 A61P5/30		
Applicant ESTETRA SPRL		

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 Ganschow, Silke Telephone No. +49 89 2399-0
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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 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>2-6, 10-15</u>
	No: Claims	<u>1, 7-9</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-15</u>
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

- 1.1 The present invention relates to a hormone replacement therapy for alleviating menopause-associated symptoms which is based on the administration to a female mammal of an estetrol component at a specific daily dose.
- 1.2 Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure.
- D1 WO 03/018026 A1 (PANTARHEI BIOSCIENCE BV [NL]; COELINGH BENNINK HERMAN JAN TI [NL]; BUN) 6 March 2003 (2003-03-06)
- D2 COELINGH BENNINK HERJAN J T ET AL: "Clinical effects of the fetal estrogen estetrol in a multiple-rising-dose study in postmenopausal women",
MATURITAS, ELSEVIER, AMSTERDAM, NL,
vol. 91, 23 June 2016 (2016-06-23), pages 93-100, XP029649879,
ISSN: 0378-5122, DOI: 10.1016/J.MATURITAS.2016.06.017
- D3 EP 3 106 148 A1 (MITHRA PHARMACEUTICALS S A [BE]) 21 December 2016 (2016-12-21)

2 Novelty

- 2.1 Document D3 teaches once daily sublingual, buccal or sublabial administration of 2-20 mg of estetrol for treating vasomotor symptoms in female hormone replacement therapy (see [0054] to [0056]). In other words, D3 discloses the administration of the specific amount of 20 mg which falls into the range of "about 15 mg to about 25 mg" according to present claim 1.
- 2.2 Thus, the content of D3 prejudices the novelty of the subject-matter of present claims 1 and 7-9.

3 Inventive step

- 3.1 D2 is considered to be the prior art closest to the subject-matter of claim 1, and discloses a daily administration of 2-40mg of estetrol for safe and effective treatment of menopausal vasomotor symptoms.
- 3.2 The technical problem is the provision of a *further treatment for menopause-associated symptoms with adequate efficacy and safety, including the determination of suitable drug dosages*.
- 3.3 The solution to this problem is seen in the use of a specific daily dose of estetrol, namely 15-25 mg. According to the application, it was surprisingly found that an optimal dose of estetrol for alleviation of VMS in postmenopausal women is of about 15-25 mg daily.
- 3.4 However, D2 already teaches that estetrol in a dose range of 2-40 mg per day improves menopausal vasomotor symptoms. According to the application, the claimed range of 15-25 mg daily allows statistically significant effects on VMS to be observed, as shown in the examples, while maintaining the treatment side effects within an acceptable window.
- Table 2 of D2 already shows a reduced number of subjects with treatment-emergent adverse events in the 20 mg E4 group compared to the 10 mg E4 group.

Page 21 (section D: measurements related to treatment side effects) of the present application shows a reduced number of adverse events in the 15 mg E4 group compared to the 10 mg E4 group. The present application is silent about any effect of 15-25 mg E4 on endometrial proliferation.

The present application does, therefore, not show any unexpected improved effect compared to D2.

- 3.5 D2 explicitly states that further separate dose-finding studies are needed for VVA and VMS to establish the optimal dose of orally administered E4 in both conditions. Carrying out dose-finding trials in respect of the envisaged treatment which identify suitable dosages are routine and cannot give rise to an inventive step.

The fact that a clinical trial may be laborious and time-consuming does not mean it is an undue burden if it is the only appropriate test, and therefore routine work. In this framework, varying the dosages of a drug, if required, in order to identify a suitable dosage cannot be considered an excessive burden. In fact, since estetrol in a dose range of 2-40 mg per day was known to improve menopausal vasomotor symptoms, it would have been obvious to vary the known dosage of estetrol to find the optimal dosage which is effective and has a minimum of side effects, as was indeed done by the applicant according to the examples of the present application.

- 3.6 As a consequence, the subject-matter of claims 1-15 does not involve an inventive step.