

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

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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/EP2020/056799

International filing date (day/month/year)
13.03.2020

Priority date (day/month/year)
15.03.2019

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/353 A61K31/4415 A61K31/593 A61K31/235 A61K31/355 A61P35/00

Applicant
LO.LI. PHARMA S.R.L.

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>4, 7, 12</u>
	No: Claims	<u>1-3, 5, 6, 8-11</u>
Inventive step (IS)	Yes: Claims	<u>4, 7</u>
	No: Claims	<u>1-3, 5, 6, 8-12</u>
Industrial applicability (IA)	Yes: Claims	<u>1-12</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

Reference is made to the following documents:

Reference is made to the following document:

- D1 US 8 221 803 B1 (PINSKI JACEK [US]) 17 July 2012 (2012-07-17)
- D2 MICHAL CIEBIERA ET AL: "Alternative Oral Agents in Prophylaxis and Therapy of Uterine Fibroids-An Up-to-Date Review",INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES,vol. 18, no. 12, 1 December 2017 (2017-12-01), page 2586, XP55641506,DOI: 10.3390/ijms18122586
- D3 CHEETHAM PHILIPPA J: "Role of Complimentary Therapy for Male LUTS",CURRENT UROLOGY REPORTS, CURRENT SCIENCE, US,vol. 14, no. 6, 13 September 2013 (2013-09-13), pages 606-613, XP035375508,ISSN: 1527-2737, DOI: 10.1007/S11934-013-0372-3[retrieved on 2013-09-13]

V.1. Medical-purpose directed claims

For the assessment of the present claims 1-12 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. The patentability can 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 product, in particular substances or compositions, for use in a first or further medical treatment.

Patentability, in particular novelty and inventive step, of claims 1-12 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

V.2. Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-3,5,6,8-11 is not new in the sense of Article 33(2) PCT in view of D1.

V.2.1. D1 (claims 1-14; column 5, lines 18-20: discloses composition for the treatment of benign prostatic hyperplasia (BPH) providing a daily dosage comprising 200-1200 IU (i.e. 5-30 micrograms) vitamin D3, 200-1200 mg ECG (also from green tea extract), alpha-tocopherol and other active ingredients, including chemotherapeutic agents, and excipients in the form of a tablet, capsule or soft gel.

Thus, D1 is prejudicial to the novelty of claims 1-3,5,6,8-11.

V.2.2. Claims limited to the use of vitamin D3 in combination with EGCG for the treatment of uterine fibroids would appear to be novel over D1.

V.3. Inventive step

The present application does not meet the criteria of patentability, because the subject-matter of claims 1-3,5,6,8-12 does not involve an inventive step.

Independent claims 1 and 9 relate to compounds/composition comprising vitamin D in combination with an agent selected from epigallocatechin gallate (EGCG), catechin, gallic acid and epicatechin gallate (ECG, for use in the prevention, control and/or treatment of a fibroid, in particular uterine fibroid, mammary fibroid, prostatic fibroid or a prostate hyperplasia.

The combination of compounds or approaches for the treatment of a disease is a matter of common practice when said compounds or approaches are already separately known to possess an activity in the treatment of that disease. Both vitamin D and EGCG are well known in the art for their beneficial effects in uterine fibroids or benign prostatic hyperplasia (BPH).

D2 (*abstract; page 3, paragraph 4 - page 6, paragraph 6) is a review document relating to oral agents for the prophylaxis and treatment of uterine fibrosis. Vitamin D and EGCG are separately reported for their beneficial effects in animal models of uterine fibroids. Moreover, this document provides a clear incentive to investigate the effects of combining EGCG with vitamin D (see page 6, last two lines of paragraph 4).

D3 (page 609, right-hand column, last paragraph - page 610, left-hand column, paragraph first; page 610, right-hand column, paragraph 3) discloses that both vitamin D and green tea/EGCG possess demonstrated activity in BPH.

The administration of vitamin D and EGCG in association would be considered as inventive only if it presents an unexpected (e.g. synergistic) effect in relation to the use of each single compound.

It is noted that the only effects demonstrated in the application relate to the treatment of uterine fibroids (myomas) using a combination of vitamin D3 and EGCG. No effects at all are demonstrated for the other types of fibroids claimed nor for the combination of vitamin D3 with the other compounds encompassed by claim 1 or 9.

It appears that the effects shown only in the treatment of myomas and only with the combination of vitamin D3 and EGCG, cannot be generalized to every and each combination encompassed by the claims, nor to each and every type of fibroids.

Therefore, no inventive step can be acknowledged to the subject-matter of claims 1-3,5,6,8-12.

V.2.3. Claims limited to the use of vitamin D3 in combination with EGCG for the treatment of uterine fibroids would appear to be inventive over the prior art.