

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/EP2016/052458	International filing date (day/month/year) 05.02.2016	Priority date (day/month/year) 06.02.2015
International Patent Classification (IPC) or both national classification and IPC INV. A61K47/14 A61K9/48		
Applicant FAES FARMA, S.A.		

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 P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Weiss, Marie-France Telephone No. +31 70 340-0 
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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, 3, 6-10, 16</u>
	No: Claims	<u>1, 4, 5, 11-15</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-16</u>
Industrial applicability (IA)	Yes: Claims	<u>1-16</u>
	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

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Prior art

Reference is made to the following documents:

- D1 EP 1 208 843 A1 (CHUGAI PHARMACEUTICAL CO LTD [JP]) 29 May 2002
- D2 WO 2008/097646 A1 (SCHERING CORP [US]; ZONG CHEN [US]) 14 August 2008
- D3 WO 2007/092755 A2 (PROVENTIV THERAPEUTICS LLC [US]; BISHOP CHARLES W [US]; CRAWFORD KEITH) 16 August 2007; *cited in the application*

2 Novelty

- 2.1 The document D1 discloses a soft capsule comprising a soft capsule shell from gelatin encapsulating an active vitamin D3 composition which may comprise a plasticiser, such as polyethylene glycol; and medium chain triglycerides.
D1 does not unambiguously disclose a soft shell capsule comprising calcifediol in combination with an organic solvent.
Therefore, the subject-matter of **claims 1-16 is new over D1** (Article 33(2) PCT).
- 2.2 The document D2 discloses compositions for which calcifediol, amongst two other active vitamin D compounds, is preferred (page 3, lines 22-23; claim 2; page 9, lines 19-20). D2 explicitly discloses the presence of a lipophilic phase. The product MIGLYOL 812, which is a medium chain triglyceride, is especially preferred as lipophilic phase (page 28, lines 15-16). The composition may be a soft capsule, including gelatin encapsulated forms (page 39, lines 6-7). Furthermore, the composition may comprise a hydrophilic phase, for which is especially preferred 1,2-propyleneglycol and/or ethanol (page 28, line 29 to page 29, line 8).
Therefore, the subject-matter of **claims 1, 4, 5, 11-15 is not new over D2** (Article 33(2) PCT).

- 2.3 The document D3 discloses a soft capsule comprising calcifediol, an oily component, an organic solvent and wax.
Therefore, the subject-matter of **claims 1-16 is new over D3** (Article 33(2) PCT).

3 Inventive step

- 3.1 D2 is considered to be the prior art closest to the subject-matter of **claim 2** and discloses a calcifediol capsule comprising a soft capsule shell from gelatin for immediate release.
- 3.2 The subject-matter of claim 2 therefore differs from this known capsule in that the soft shell additionally comprises a plasticizer.
- 3.3 The technical effect resulting from said difference is well-known to the skilled person, namely to adapt the softness of the shell of a capsule.
- 3.4 The problem to be solved by the present invention may therefore be regarded as to provide an alternative calcifediol soft shell capsule formulation.
- 3.5 The solution proposed in **claim 2** of the present application cannot be considered to involve an inventive step (Article 33(3) PCT), the reasons being explained as follows. The skilled person would easily be in a position to add any plasticizers to a soft capsule of calcifediol in order to arrive at an alternative capsule.
- 3.6 For none of the remaining novel claims (claims 3, 6-10, 16) a technical effect is shown in the present application. Therefore, none of said claims are considered to involve an inventive step according to Article 33(3) PCT.
- 3.7 A technical effect is shown in example 3 of the present application for the compositions given in example 1. Accordingly, claim 3 - when taking out the "and/or" combination - may be considered to show said effect.

Re Item VIII

Certain observations on the international application

Claim 12 does not meet the requirement of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved, namely in the form of specific *in vivo* release characteristics/ pharmacokinetic parameters. Such a definition is not allowable.

In addition, said *in vivo* release characteristics/pharmacokinetic parameters, although measurable by the skilled person, are not suitable for unambiguous characterization of a composition (formulation, dosage form...) due to the inherent variation among

different subjects and different testing conditions, which make it impossible to distinguish the subject-matter claimed from the prior art. As a result, the application does not comply with the requirements of Article 6 PCT.