

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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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/EP2015/073190	International filing date (day/month/year) 07.10.2015	Priority date (day/month/year) 08.10.2014
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International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/00 A61K9/16 A61K31/167 A61K31/58

Applicant
ZAMBON S.P.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 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 Giró, Annalisa 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>1-9</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-9</u>
Industrial applicability (IA)	Yes: Claims	<u>1-9</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

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

Reference is made to the following documents:

- D1 WO 2013/109220 A1 (BILGIC MAHMUT [TR]) 25 July 2013 (2013-07-25)
- D2 WO 2011/093817 A1 (BILGIC MAHMUT [TR]) 4 August 2011 (2011-08-04)
- D3 EP 2 682 098 A2 (ARVEN ILAC SANAYI VE TICARET A S [TR]) 8 January 2014 (2014-01-08)
- D4 WO 2007/045689 A2 (ERATECH S R L [IT]; VENEZIANI CRISTINA [IT]; CAPONETTI GIOVANNI [IT];) 26 April 2007 (2007-04-26)
- D5 EP 1 086 697 A2 (ASTRAZENECA AB [SE]) 28 March 2001 (2001-03-28) cited in the application
- D6 WO 00/33789 A2 (R P SCHERER INC [US]; EMBLETON JONATHAN KENNETH [CH]) 15 June 2000 (2000-06-15)
- D7 WO 03/024396 A2 (GLAXO GROUP LTD [GB]; BROWN ANDREW BRUCE [US]; VAN OORT MICHAEL MARY []) 27 March 2003 (2003-03-27)
- D8 WO 2014/167028 A1 (ZAMBON SPA [IT]) 16 October 2014 (2014-10-16)

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

1. Novelty (Article 33(2) PCT).

1.1 As a preliminary remark, it is noted that, although the composition of claim 1 is defined as comprising a first, a second and a third powder, this is merely a conceptual separation of the ingredients, corresponding to the materials used to prepare said

composition. In the final claimed powder, the ingredients are in fact physically mixed with each other. Therefore, the subject-matter addressed by claim 1 corresponds to a powder composition comprising budesonide or a salt thereof, formoterol or a salt thereof, leucine, a first lactose with a X50 of 35-75 microns (coarse lactose) and a second lactose with a X50 of 1.5 to 10 microns (fine lactose), all components present respectively in amounts to be calculated on the basis of the corresponding claimed amounts and ratios.

2.2 None of the cited prior art documents discloses the composition described under point 1.1.

D1, D2 and D3 disclose powder compositions comprising budesonide, formoterol and a first lactose with a X50 of 35-75 microns and a second lactose with a X50 of 1.5 to 10 microns, all in amounts falling within the ranges claimed in present claim 1. Said compositions do not comprise leucine.

D4 discloses powder compositions comprising budesonide or formoterol, leucine and lactose. D4 does not disclose the combination of budesonide and formoterol, nor the presence of a coarse and a fine lactose.

D5 discloses powder compositions comprising budesonide in combination with formoterol and lactose. No leucine, nor the mixture of a coarse and a fine lactose are present in the compositions.

D6 and D7 disclose powder compositions for inhalation comprising an active ingredient, leucine and a mixture of a coarse and a fine lactose. Said compositions do not comprise the combination of budesonide and formoterol.

Therefore, the subject-matter of claim 1, and consequently also of claims 2-9, appears to be novel over said documents in the sense of Article 33(2) PCT.

2. Inventive Step (Article 33(3) PCT).

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-9 does not involve an inventive step in the sense of Article 33(3) PCT.

2.1 D1 is regarded as being the prior art closest to the subject-matter of independent claim 1. As mentioned above, D1 discloses powder formulations comprising budesonide, formoterol, coarse lactose particles, fine lactose particles. The X50 values of said particles fall within the claimed ranges, as well as the amounts of all components.

The subject-matter of claim 1 therefore differs from D1 in the presence of leucine.

According to the present application, leucine is added to the formulation as hydrophobic substance in order to reduce the sensitivity to humidity of the whole formulation and to facilitate particles disaggregation (see page 13, lines 1-2).

The problem to be solved by the present invention could therefore be regarded as how to provide improved powder compositions.

Leucine, however, appears to be an excipient of choice in powder formulations for inhalation (see, e.g., D4, D6, D7). D4, in particular, explicitly suggests its utility as hydrophobic substance which is able to reduce sensitivity to humidity and to facilitate particle disaggregation.

Thus, the solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT).

2.2 Also D5 could be considering as stating point in the analysis of inventive step for present claim 1. As mentioned above, D5 discloses powder compositions comprising the combination of budesonide with formoterol for use in inhalation therapy. The subject-matter of claim 1 therefore differs from the disclosure of D5 in that a mixture of a coarse and a fine lactose are present in the compositions.

The idea of formulating powders for inhalation by mixing fine lactose carrier particles (known as respirable fraction) with coarse lactose carrier particles (known as non-respirable fraction) is however a very well-established practice in the art (see, e.g., D1-D3, D6 and D7). In particular, D1-D3, D6 and D7 disclose the choice of coarse lactose particles and fine lactose particles having sizes falling within the claimed X50 ranges.

Therefore, also this aspect of the present invention cannot be regarded as justifying the presence of an inventive step for the subject-matter of present claim 1 (Article 33 (3) PCT).

2.3 As all cited documents disclose that the powder formulations mentioned therein are filled into a device for inhalation, thereby resulting in a kit, the objections mentioned above apply also to the subject-matter of independent claim 9, which is therefore considered not inventive.

2.4 Dependent claims 2-8 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and inventive step.

Furthermore, it should be noticed that said dependent claims are only allowable in combination with independent claims meeting the requirements of the PCT in regard to novelty and inventive step.

3. Industrial applicability (Article 33(4) PCT).

Claims 1-9 are industrial applicable in the sense of Article 33(4) PCT.

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 (<i>valid claim</i>) (day/month/year)
WO2014/167028	16.10.2014	09.04.2014	10.04.2013

Re Item VIII

Certain observations on the international application

The application does not meet the requirements of Article 6 PCT, because the subject-matter of claim 1 is not clear for the following reason.

As also apparent from the description (see page 15, lines 20-27), the features "fine particle fraction" (FPF) and "delivered fraction" (DF) mentioned in claim 1 relate to methods of using the claimed composition (at delivery from inhaler) rather than clearly defining the composition in terms of its technical features. The intended limitations are therefore not clear from this claim and said features are not regarded as technical features further limiting the scope of the claim.