

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

ZBM PATENTS
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NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing (day/month/year) 24 July 2014 (24-07-2014)
Applicant's or agent's file reference P2706PC00	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/EP2014/061735	International filing date (day/month/year) 5 June 2014 (05-06-2014)
Applicant FERRER INTERNACIONAL, S.A.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

How? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within **19 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the International Searching Authority



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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P2706PC00	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2014/061735	International filing date (<i>day/month/year</i>) 5 June 2014 (05-06-2014)	(Earliest) Priority Date (<i>day/month/year</i>) 6 June 2013 (06-06-2013)
Applicant FERRER INTERNACIONAL, S.A.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out 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))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*b/s(a)*).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
 b. ☒ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2014/061735

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/50 A61K31/40 A61K31/403 A61K31/60 A61P9/00
 ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/118359 A2 (FERRER INTERNAC SA [ES]; FUNDACION CT NAC DE INVESTIGAC [ES]; GUERRERO) 1 October 2009 (2009-10-01)	1-17
Y	page 10, line 31 - page 11, line 27 examples	1-17
X	WO 2011/096665 A2 (HANMI HOLDINGS CO LTD [KR]; WOO JONG SOO [KR]; PARK JAE HYUN [KR]; KIM) 11 August 2011 (2011-08-11)	1-17
Y	cited in the application page 3, lines 10-25 page 5, lines 21-26 page 7, lines 7-12 page 10, comparative examples 1, 2 in table 3 pages 13-14, table 7 pages 16-17, tables 9 and 10 ----- -/-	1-17

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 July 2014

Date of mailing of the international search report

24/07/2014

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Rodríguez-Palmero, M

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2014/061735

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2012/045505 A1 (SASMAL BADAL KUMAR [IN] ET AL) 23 February 2012 (2012-02-23) page 2, paragraph 0018 examples 3,4 -----	1-17
Y	WO 2006/000052 A1 (SMITH HOWARD J & ASS PTY LTD [AU]; SMITH HOWARD J [AU]) 5 January 2006 (2006-01-05) example 2 -----	1-17
Y	US 2003/049314 A1 (LIANG MATTHEW H [US] ET AL) 13 March 2003 (2003-03-13) page 7, paragraph 0079 examples 1,2 -----	1-17
Y	WO 03/020243 A1 (LONGWOOD PHARMACEUTICAL RES IN [US]) 13 March 2003 (2003-03-13) page 15, lines 22-25 page 21, lines 23-33 examples 5,6 -----	1-17
Y	US 2012/027849 A1 (KHAMAR BAKULESH MAFATLAL [IN] ET AL) 2 February 2012 (2012-02-02) example 7 -----	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2014/061735

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009118359	A2	01-10-2009	AR 071094 A1 26-05-2010
		AU 2009228832 A1 01-10-2009	
		CA 2720800 A1 01-10-2009	
		CN 101980701 A 23-02-2011	
		CO 6311069 A2 22-08-2011	
		EC SP10010562 A 29-04-2011	
		EP 2273985 A2 19-01-2011	
		HN 2010001979 A 01-07-2013	
		IS 8932 A 05-10-2010	
		JP 2011515445 A 19-05-2011	
		KR 20110007602 A 24-01-2011	
		MA 32347 B1 01-06-2011	
		NZ 588239 A 30-09-2011	
		RU 2010144131 A 10-05-2012	
		SV 2010003684 A 31-03-2011	
		TW 200944251 A 01-11-2009	
		UA 99758 C2 25-09-2012	
		US 2011086094 A1 14-04-2011	
		UY 31741 A 14-12-2009	
		WO 2009118359 A2 01-10-2009	
WO 2011096665	A2	11-08-2011	AR 080023 A1 07-03-2012
		CN 102740857 A 17-10-2012	
		EP 2531199 A2 12-12-2012	
		JP 2013518873 A 23-05-2013	
		KR 20110090060 A 10-08-2011	
		TW 201141487 A 01-12-2011	
		US 2012301549 A1 29-11-2012	
		WO 2011096665 A2 11-08-2011	
US 2012045505	A1	23-02-2012	AU 2010242938 A1 17-11-2011
		EP 2424509 A2 07-03-2012	
		NZ 596064 A 28-03-2014	
		US 2012045505 A1 23-02-2012	
		WO 2010127205 A2 04-11-2010	
WO 2006000052	A1	05-01-2006	CA 2571447 A1 05-01-2006
		EP 1784193 A1 16-05-2007	
		US 2009098201 A1 16-04-2009	
		WO 2006000052 A1 05-01-2006	
US 2003049314	A1	13-03-2003	NONE
WO 03020243	A1	13-03-2003	AT 530167 T 15-11-2011
		CA 2461958 A1 13-03-2003	
		CN 1575162 A 02-02-2005	
		CN 101642459 A 10-02-2010	
		EP 1429729 A1 23-06-2004	
		ES 2307463 T1 01-12-2008	
		IL 160643 A 17-02-2010	
		JP 2005504064 A 10-02-2005	
		JP 2009256381 A 05-11-2009	
		JP 2013006857 A 10-01-2013	
		KR 20040037075 A 04-05-2004	
		NZ 532014 A 23-12-2005	
		US 2003068366 A1 10-04-2003	
		WO 03020243 A1 13-03-2003	
		ZA 200402417 A 29-03-2005	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2014/061735

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2012027849 A1	02-02-2012	AU 2010212580 A1	29-09-2011
		CA 2754134 A1	19-08-2010
		CN 102480954 A	30-05-2012
		EP 2395838 A1	21-12-2011
		GB 2482432 A	01-02-2012
		NZ 595127 A	30-08-2013
		US 2012027849 A1	02-02-2012
		WO 2010092450 A1	19-08-2010

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/EP2014/061735

International filing date (day/month/year)
05.06.2014

Priority date (day/month/year)
06.06.2013

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/50 A61K31/40 A61K31/403 A61K31/60 A61P9/00

Applicant
FERRER INTERNACIONAL, 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
D-80298 Munich
Tel. +49 89 2399 - 0
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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Rodríguez-Palmero, M

Telephone No. +49 89 2399-7871



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 filed or furnished:
- a. (means)
- ☐ on paper
 - ☐ in electronic form
- b. (time)
- ☐ in the international application as filed
 - ☐ together with the international application in electronic form
 - ☐ subsequently to this Authority for the purposes of search
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 in 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>1-17</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-17</u>
Industrial applicability (IA)	Yes: Claims	<u>1-17</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 Documents

1.1 Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure:

- D1 WO 2009/118359 A2 (FERRER INTERNAC SA [ES]; FUNDACION CT NAC DE INVESTIGAC [ES]; GUERRERO) 1 October 2009 (2009-10-01)
- D2 WO 2011/096665 A2 (HANMI HOLDINGS CO LTD [KR]; WOO JONG SOO [KR]; PARK JAE HYUN [KR]; KIM) 11 August 2011 (2011-08-11)cited in the application
- D3 US 2012/045505 A1 (SASMAL BADAL KUMAR [IN] ET AL) 23 February 2012 (2012-02-23)
- D4 WO 2006/000052 A1 (SMITH HOWARD J & ASS PTY LTD [AU]; SMITH HOWARD J [AU]) 5 January 2006 (2006-01-05)
- D5 US 2003/049314 A1 (LIANG MATTHEW H [US] ET AL) 13 March 2003 (2003-03-13)
- D6 WO 03/020243 A1 (LONGWOOD PHARMACEUTICAL RES IN [US]) 13 March 2003 (2003-03-13)

1.2 Unless indicated, reference is made to the passages indicated in the international search report.

2 Clarity (Art. 6 PCT)

2.1 The term "substantially free" in present claim 1 is not considered to be clear (Art. 6 PCT). The person skilled in the art does not know which amounts of water-insoluble polymer or enteric polymer can be included in the composition to be still considered "substantially free" of these compounds. For the present opinion, it will be considered that the composition is free of these polymers.

- 2.2 Present claim 1 mentions the exclusion of water-insoluble polymers or enteric polymers (see item 2.1 above). It is mentioned in page 11, lines 1-2 that water-insoluble polymers include waxes such as carnauba wax, glyceryl monostearate, glyceryl monooleate and beeswax. However, these compounds are not polymers. This results in an inconsistency between the claim and the description, contrary to Art. 6 PCT. For the purpose of the present opinion, the wording of the claim has been taken into consideration only.

3 Novelty (Art. 33(2) PCT)

None of the cited prior art documents disclose a dosage form as defined in present claim 1. Consequently, the subject-matter claimed is novel over those prior art documents.

4 Inventive Step (Art. 33(3) PCT)

- 4.1 D1 concerns combinations for the prevention of cardiovascular diseases comprising acetylsalicylic acid, HMG-CoA reductase inhibitors and ACE inhibitors. The active ingredients are present in independent coated tablets, a fact that prevents incompatibility between the different components. The coating comprises a film-forming agent, such as a film-forming polymer, e.g. partially hydrolysed polyvinyl alcohol. The compositions of the examples disclosed therein comprise Opadry® AMB with the OY-B-28920 as coating of the acetylsalicylic acid (ASA) tablets (see example 1). This coating appears to be present in an amount of above 6 mg/cm², although this feature is not explicitly mentioned therein.

This document is considered the closest prior art for the present claimed subject-matter.

The only difference of the present claimed subject-matter with D1 is the presence of two or more single separate coated dosage units comprising ASA.

This feature, however, is not shown in the present application to contribute to solve the problem of the stability of the combined composition, which is the problem to be solved mentioned in the present application (see p. 1, l. 7-10; p. 3, l. 13-17).

Features which cannot be seen to make any contribution, either independently or in combination with other features, to the technical character of an invention are not relevant for assessing inventive step.

Consequently, the problem can only be considered to provide an alternative composition to that of D1.

D2 provides a complex formulation for the prevention or treatment of cardiovascular diseases, with improved storage stability by preventing the deterioration in the stability of HMG-CoA reductase inhibitors which is caused by salicylic acid. The formulation comprises (1) an aspirin granule or pellet which is coated with a barrier containing a hydrophobic additive; (2) an HMG-CoA reductase inhibitor granule or pellet. These two components are filled in a capsule or compressed.

D3 provides pharmaceutical compositions which comprise a cholesterol-lowering agent, an inhibitor of the renin-angiotensin system, aspirin, and a beta-adrenergic receptor blocker or diuretic, which are useful in treatment or reduction of risk of cardiovascular events, and with minimal or no physico-chemical incompatibility between the active agents. In examples 3 and 4 a simvastatin tablet, an ASA tablet and a lisinopril tablet are combined in a capsule. The ASA tablet is coated with Opadry®, i.e. polyvinyl alcohol. Paragraph [0030] mentions the possibility of combining the different active agents in the form of pellets, granules, mini-tablets, etc.

D4 discloses a formulation comprising (1) coated aspirin seeds using HPMC EUDRAGIT NE 30D polymer coatings (2) simvastatin granules to provide a unit dose form comprising 50 mg of aspirin and 5 mg of simvastatin.

D5 discloses capsules comprising aspirin in enteric coated granules combined with granules of pravastatin and ramipril.

D6 teaches compositions comprising aspirin, pravastatin and ramipril all separately present in coated or enterically coated granules or beads or tablets.

D2-D6 all provide compositions combining ASA and HMG-CoA dosage units in which 2 or more ASA dosage units are included. These documents thus show that the presence of two or more single separate coated dosage units in the form of granules, pellets, etc. is considered customary practice in the field of galenics. The fact that two separated dosage units have a better dissolution profile is also common knowledge.

Consequently, the subject-matter claimed is considered obvious in the light of D1 either alone or in combination with any of D2-D6.

Even when the amount of coating in D1 was shown to be below the amount mentioned in present claim 1, it is considered that increasing the amount of coating is one of the straightforward possibilities that the person skilled in the art would select, depending on the circumstances, without exercising inventive skill, in order to solve the problem posed, especially as the advantages thus achieved can be readily contemplated in advance.

For all these reasons, an inventive step of the claimed subject-matter cannot be acknowledged.

- 4.2 Alternatively, D2 can also be considered closest prior art for the present claimed subject-matter. In particular, in table 6 on p. 12, the formulation examples 1-4, 6 (comprising carnauba wax in the coating for the ASA dosage units, but no water-insoluble/enteric polymer) and comparative formulation examples 1, 2 (coating of HPMC for ASA dosage units, no waxes) are close to the present claimed subject-matter. The difference is that the granules containing the HMG-CoA reductase inhibitor are not coated therein. All the compositions mentioned above are shown therein to provide stability in the formulation, compared to comparative formulation example 7 with no barrier (see table 7 on pages 13-15). The present application does not show that the presence of an additional coating on the HMG-CoA including dosage units provides an advantage over those without. Moreover, other documents teach that the dosage units comprising HMG-CoA can also be coated (see D1 and D6). Consequently, an inventive step cannot be recognised over D2 either taken alone or in combination with D1/D6.

5 Industrial applicability (Art. 33(4) PCT)

Present claims 1-17 are susceptible of industrial application and thus do not contravene Art. 33(4) PCT.

Re Item VIII

Certain observations on the international application

- 6 The term "esters" in connection with ACE inhibitors in claims 16 and 17 renders their scope unclear, since it is not known to the skilled reader which structures are intended to be encompassed by this term.