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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: PI.-F. HOFFMANN-LA ROCHE AG.-Solicitud de Patente de Invención en Fase Nacional PCT para "COMPOSICIONES FARMACÉUTICAS QUE COMPRENDEN UN PROFÁRMACO INHIBIDOR DE POLIMERASA DE HCV".-Clase A61K 9/20.-Expediente número 11-082.167.-

1. Me refiero a mi memorial de 12 de Septiembre de 2011.
2. Atentamente me permito presentar a ese Despacho el Reporte Preliminar Internacional sobre Patentabilidad expedido el 26 de Septiembre de 2011 correspondiente a la solicitud internacional PCT/EP2010/050182, actualmente en trámite de Fase Internacional bajo el número de la referencia.
3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,

ALICIA LLORED A RICAURTE

T.P. 53.215

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 25249	FOR FURTHER ACTION See Form PCT/PEA/416	
International application No. PCT/EP2010/050182	International filing date (day/month/year) 11.01.2010	Priority date (day/month/year) 21.01.2009
International Patent Classification (IPC) or national classification and IPC INV. A61K9/20		
Applicant F.HOFFMANN-LA ROCHE AG et al		
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>7</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☐ (sent to the applicant and to the International Bureau) a total of sheets, as follows: ☐ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in Item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3bis of Annex C of the Administrative Instructions).		
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ 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 Article 35(2) with regard to novelty, inventive step or 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		
Date of submission of the demand	Date of completion of this report	
11.11.2010	26.09.2011	
Name and mailing address of the international preliminary examining authority:  European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016		Authorized officer Telephone No. +31 70 340-0 

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Box No. I Basis of the report

1. With regard to the language, this report is based on

- ☒ 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 (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))

2. With regard to the elements* of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-23 as originally filed

Claims, Numbers

1-24 as originally filed

Drawings, Sheets

1/8-8/8 as originally filed

- ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify)*:
- ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify)*:

5. ☐ This report has been established:

- ☐ taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
- ☐ without taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).

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6. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-24</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-24</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-24</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

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

Cited documents

Reference is made to the following documents:

- D1 WO 2007/065829 A1 (HOFFMANN LA ROCHE; PHARMASSET INC),
cited in the application, 14 June 2007
- D2 US 2007/202175 A1 (AHMED ET AL) 30 August 2007
- D3 DE FRANCESCO ET MIGLIACCIO: "Challenges and successes in
developing new therapies for hepatitis C", NATURE, vol. 436, pages
953-960, XP002635205, DOI: 10.1038, 18 August 2005

Patentability

Claim 22 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT.

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow 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 claim 22 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

Novelty

Claim 24 is a so called omnibus claim and does not meet the requirements of Article 6 and Rule 6.2a PCT (see below under item VIII for reasoned statement). In the following claim 24 is discussed in as far as it can be considered to cover the same subject-matter as claims 1-23, i.e. as if its scope was identical to that of independent claim 1.

Document D1 discloses acylated pyrimidine nucleosides which are prodrugs of an inhibitor of hepatitis C virus RNA-dependent RNA viral polymerase, such as isobutyric acid (2R,3R,4R,5R)-5-(4-amino-2-oxo-2H-pyrimidin-1-yl)-4-fluoro-3-isobutyryloxy-4-methyl-tetrahydro-furan-2-yl methyl ester (cf. p. 1 lines 1-2, example 2).

Pharmaceutical compositions are provided comprising the compounds of D1 admixed with at least one pharmaceutical acceptable carrier, diluent or excipient (cf. p. 15 lines 26-28).

Document D2 relates to a pharmaceutical composition comprising a solid dispersion prepared by hot melt extrusion of isobutyric acid (2R,3S,4R,5R)-5-(4-amino-2-oxo-2H-pyrimidin-1-yl)-2-azido-3,4-bis-iso-butyryloxy-tetrahydro-furan-3-yl methyl ester hydrochloride salt and a PEG/polypropylene glycol (PPG) block copolymer useful in the therapy of hepatitis C virus (cf. paragraphs 0002, 0013).

Document D3 reviews the progress in the identification of new targets towards the treatment of chronic hepatitis C virus infection, including selective inhibitors of the NS5B viral polymerase such as nucleoside analogues (cf. p. 953 column 2 paragraphs 1, 2 figure 2).

The subject-matter of independent claims 1 and 22 differs from D1, D2 and D3 in the presence of hydroxypropylcellulose in the formulation. Additionally, the subject-matter of claims 1 and 22 differs from D2 and D3 in the selection of the active ingredient. Therefore, the subject-matter of claims 1-24 of the present application is new in the meaning of Article 33(2) PCT.

Inventive step

Document D1 is considered as the closest prior art to the subject-matter of the present application.

D1 deals with acylated pyrimidine nucleosides prodrugs which are inhibitors of HCV replication and which provide improved drug absorption when administered orally (cf. p. 1 lines 8-11). Solid form preparations of the prodrugs of D1 include tablets and dispersible granules in which the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired (cf. p. 26 lines 5-12).

The subject-matter of **independent claim 1** of the present application differs from D1 in that hydroxypropylcellulose is present in the pharmaceutical composition and in the percentage composition of the active principle and excipients.

The technical effect of these differences is to obtain superior densification properties for low bulk density drugs with reasonable granule growth.

Therefore, in view of D1, the objective technical problem underlying the present application can be considered as to provide a pharmaceutical composition of a hepatitis C virus polymerase inhibitor prodrug with improved compression and flow and fast dissolution profiles.

From D1 it is known the use of several solid carriers such as methylcellulose or sodium carboxymethylcellulose among other excipients to form solid form preparations (cf. p. 26 lines 12-17). In D1, a typical preparation will contain from 5% to 95% of active compound (cf. p. 25 lines 11-12). There is no hint for the skill person starting from D1, to try an amount from 1%w/w to 4%w/w of hydroxypropylcellulose as binding agent to obtain granules of the active compound with adequate density and particle size arriving to the subject-matter of claim 1. Consequently, the subject-matter of claim 1 involves an inventive step (Article 33(3) PCT).

Claims 2-24 depend on or refer to claim 1 and as such also meet the requirements of the PCT with respect to inventive step.

Industrial Applicability

The subject-matter of claims 1-24 is considered to meet the requirements of industrial applicability, therefore the present application meets the criteria of Article 33(4) PCT.

Re Item VIII

Certain observations on the international application

The term "about" used in connection with ranges in claims 1-5 and 18 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.

Claim 24 is an omnibus claim which relies on references to the description in respect to all its technical features and therefore contravenes the requirements of Article 6 in conjunction with rule 6.2a PCT. The vague and imprecise statement "the invention as hereinbefore described" in claim 24 leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear. This statement should therefore be amended to remove this inconsistency.

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The vague and imprecise statement in the description on page 23 lines 7-12 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in a lack of clarity of the claims (Article 6 PCT) when the description is used to interpret the claims. This statement should therefore be amended to remove this inconsistency.