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Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
19 November 2015

WO 2015/145415 A3

(54) Title: IBRUTINIB SOLID FORMS AND PRODUCTION PROCESS THEREFOR

(57) Abstract: Provided are ibrutinib polymorphs, e.g., crystalline ibrutinib Forms III, IV, V, VI, VII, VIII and Form IX and processes for producing these crystalline forms, stable amorphous ibrutinib and processes for preparing stable amorphous ibrutinib, pharmaceutical compositions comprising these forms and methods of using these crystalline and amorphous forms.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL15/00017

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 487/04; A61K 45/06 (2015.01)
CPC - A61K 9/2013, 9/2054
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)
IPC(8): C07D 487/04; A61K 45/06 (2015.01)
CPC: A61K 9/2013, 9/2054

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)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); ProQuest; Scifinder; Google/Google Scholar; KEYWORDS: crystalline, ibrutinib, diffraction, DSC, solvent, toluene, anisole

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2013/0338172 A1 (SMYTH, M et al.) 19 December 2013; paragraphs [0007], [0037]-[0038], [0053], [0080], [0447], [0449], [0542]-[0545], [0551], [0557], [0624]-[0626]	1-3, 7-11, 17/7, 18/7, 19/7, 20-21, 24-25, 48-51
A	US 2014/0079690 A1 (PHARMACYCLICS, INC.) 20 March 2014; entire document	1-3, 7-11, 17/7, 18/7, 19/7, 20-21, 24-25, 48-51
A	WO 2014/004707 A1 (PRINCIPIA BIOPHARMA INC.) 03 January 2014; entire document	1-3, 7-11, 17/7, 18/7, 19/7, 20-21, 24-25, 48-51
A	US 2013/0041014 A1 (LAVITRANO, M et al.) 14 February 2013; entire document	1-3, 7-11, 17/7, 18/7, 19/7, 20-21, 24-25, 48-51

☐ 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	Date of mailing of the international search report
18 June 2015 (18.06.2015)	24 SEP 2015
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL15/00017

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-3, 7-11, 17/7, 18/7, 19/7, 20-21, 24-25, and 48-51 are directed toward crystalline ibrutinib Form VII.
Group II: Claims 4-6, 12-16, 17/12, 18/12, 19/12, and 22-25 are directed toward crystalline ibrutinib Form VIII.
Group III: Claims 26-30 are directed toward crystalline ibrutinib Form III.
Group IV: Claims 31-39, 85-86 and 88-89 are directed toward crystalline ibrutinib Form IV.
Group V: Claims 40-44, 85-86 and 88-89 are directed toward crystalline ibrutinib Form V.
Group VI: Claims 45-47 are directed toward crystalline ibrutinib Form VI.
Group VII: Claims 52-56 are directed toward crystalline ibrutinib Form IX.
Group VIII: Claims 57-89 are directed toward amorphous ibrutinib.

-***-Continued Within the Next Supplemental Box-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 7-11, 17/7, 18/7, 19/7, 20-21, 24-25, and 48-51

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL15/00017

-***-Continued from Box III: Observations where unity of invention is lacking -***-

The inventions listed as Groups I-VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
the special technical features of Group I include crystalline ibrutinib Form VII, characterized by an X-ray powder diffraction pattern exhibiting strong diffraction peaks at 6.5, 13.0, 17.7, 18.3, 20.0, 21.0, 21.5, and 23.9, which are not present in Groups II-VIII;
the special technical features of Group II include crystalline ibrutinib Form VIII, characterized by an X-ray powder diffraction pattern exhibiting strong diffraction peaks at 7.7, 15.3, 19.4 and 24.0, which are not present in Groups I and III-VIII;
the special technical features of Group III include crystalline ibrutinib Form III, characterized by an X-ray powder diffraction pattern exhibiting strong diffraction peaks at 17.90, 19.50, 20.10 and 21.02, which are not present in Groups I-II and IV-VIII;
the special technical features of Group IV include crystalline ibrutinib Form IV, characterized by an X-ray powder diffraction pattern exhibiting strong diffraction peaks at 17.30, 20.10, 21.30 and 22.06, which are not present in Groups I-III and V-VIII;
the special technical features of Group V include crystalline ibrutinib Form V, characterized by an X-ray powder diffraction pattern exhibiting strong diffraction peaks at 6.26, 9.98, 18.06, 19.78 and 22.94, which are not present in Groups I-IV and VI-VIII;
the special technical features of Group VI include crystalline ibrutinib Form VI, characterized by an X-ray powder diffraction pattern exhibiting strong diffraction peaks at 6.74, 10.34, 17.94 and 21.46, which are not present in Groups I-V and VII-VIII;
the special technical features of Group VII include crystalline ibrutinib Form IX, characterized by an X-ray powder diffraction pattern exhibiting strong diffraction peaks at 9.6, 10.5, 17.7, 18.3, 20.0, 21.0 and 21.4, which are not present in Groups I-VI and VIII; and
the special technical features of Group VIII include amorphous ibrutinib, and mixing an ibrutinib solution with silica, filtering the silica out loading the solution onto a chromatographic column, eluting the ibrutinib from the column, optionally concentrating the eluting solution, and spray drying the solution to give amorphous ibrutinib, which are not present in Groups I-VII.

The common technical features of Groups I-II are preparing crystalline ibrutinib, dissolving or slurrying ibrutinib in a solvent and isolating the solid; a pharmaceutical composition comprising crystalline ibrutinib and pharmaceutically acceptable additives and excipients; and the use of ibrutinib for the treatment of Mantle Cell Lymphoma.

These common technical features are disclosed by US 2014/0079690 A1 to Pharmacyclics, Inc. (hereinafter 'Pharmacyclics'). Pharmacyclics discloses preparing crystalline ibrutinib, dissolving or slurrying ibrutinib in a solvent and isolating the solid (compound of Formula I is Ibrutinib and is isolated using crystallization; paragraphs [0038], [0395], [0409]); a pharmaceutical composition comprising crystalline ibrutinib and pharmaceutically acceptable additives and excipients (pharmaceutical composition comprising Ibrutinib and pharmaceutically acceptable additives; paragraphs [0038], [0392], [0519], [0530]); and the use of ibrutinib for the treatment of Mantle Cell Lymphoma (use of compound is treat mantle cell lymphoma; paragraphs [0157], [0159]).

Since the common technical features are previously disclosed by Pharmacyclics, these common features are not special and so Groups I-VIII lack unity.