PTO-1382 (Rev. 04-2010)
Approved for use through 04/30/2013. OMB 0651-0021
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL LETTER TO THE UNITED STATES RECEIVING OFFICE

Express Mail mailing number: N/A	Date of deposit: 26 June 2013
File reference no.: 11913-1013	International application no. (if known): Not Yet Assigned
Customer Number[1]: 22,852	Earliest priority date claimed (Day/Month/Year): 29 June 2012
Title of the invention: FORMULATIONS	

[1] **Customer Number will allow access to the application in Private PAIR but cannot be used to establish or change the correspondence address.**

[X] **This is a new International Application**

SCREENING DISCLOSURE INFORMATION

In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (check as boxes as apply):

[ ] The invention disclosed was **not** made in the United States of America.

[ ] There is no prior U.S. application relating to this invention.

[X] The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. *(NOTE: priority to these applications may or may not be claimed on the Request (form PCT/RO/101) and this listing does **not** constitute a claim for priority.)*

application no.	61/666,562	filed on	29 June 2012
application no.		filed on	

[X] The present international application contains additional subject matter not found in the prior U.S. application(s) identified above. The additional subject matter is found on pages throughout and [X] **DOES NOT ALTER** [ ] **MIGHT BE CONSIDERED TO ALTER** the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 C.F.R. 5.15.

Itemized list of contents

Sheets of Request form: 5	Check no.: N/A
Sheets of description (excluding sequence listing): 39	Return receipt postcard: N/A
Sheets of claims: 4	Power of attorney: N/A
Sheets of abstract: 1	Certified copy of priority document (specify): To be prepared and transmitted to the International Bureau by the RO/US
Sheets of drawings: N/A	Other (specify): 1. PCT Calculation Sheet (PCT-SAFE [EASY mode]) 2. Validation Messages Sheet (PCT-SAFE [EASY mode])
Sheets of sequence listing: N/A	
Sequence listing diskette/CD: N/A	

The person signing this form is:	[ ] Applicant	
	[X] Attorney/Agent (Reg. No.) 71,542	RODRIGO, Christina M. Name of person signing
	[ ] Common Representative	/Christina M. RODRIGO, Reg. No. 71,542/ Signature

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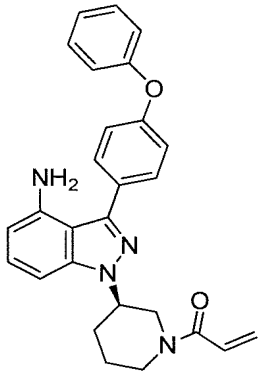
FORMULATIONS

The present disclosure provides certain oral pharmaceutical formulations of ibrutinib, certain methods for their administration, certain processes of their production, and certain uses of these formulations for the treatment of diseases treatable by ibrutinib such as cancer, inflammatory diseases, and autoimmune diseases.

Bruton's tyrosine kinase (BTK) is a member of the Tec tyrosine kinase family. BTK is expressed in most hematopoietic cells such as B cells, mast cells, and macrophages, but not in T cells, natural killer cells, and plasma cells. BTK plays a role in the development and activation of B cells. Mutations in the human BTK gene cause the inherited disease X-linked agammaglobulinemia (XLA), with lack of peripheral B cells and low levels of serum Ig. In XLA, the primary immune deficit is B cell specific. The development of drugs which inhibit BTK can have therapeutic significance in the treatment of both B cell-related hematological cancers (e.g. non-Hodgkin lymphoma (NHL) and B cell chronic lymphocytic leukemia (B-CLL), and autoimmune diseases (e.g. rheumatoid arthritis, Sjogrens syndrome, IBD, lupus, and asthma).

PCI-32765 (ibrutinib) is disclose d in U.S. Patent No. 7,514,444, issued on April 7, 2009, and has the following structure:



Ibrutinib is an orally available drug that targets Bruton's tyrosine kinase (BTK). Ibrutinib is an irreversible small molecule BTK inhibitor that is in Ph Ib/II of clinical trials in a variety of B-cell malignancies including chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL) and multiple myeloma (cancer of plasma cells, a type of white blood cell present in bone marrow). At present ibrutinib is administered orally in clinical trials, via the gastrointestinal tract, at high clinical doses (420 mg/day or 840 mg/day) to patients with CLL and SLL to obtain the desired thereapeutic effect. The need for such high doses of ibrutinib

may be due to low bioavailability (the oral bioavailability of ibrutinib is reported to be 22.8% in rats) and may be responsible for the adverse side effects associated with the use of ibrutinib such as nausea or emesis, dizziness and diarrhea. Moreover, low bioavailability results in more variable absorption and potential variability of the desired therapeutic response.

As stated above, at present ibrutinib is administered orally, via the gastrointestinal tract, at high clinical doses (420 mg/day or 840 mg/day) to patients to obtain the desired clinical benefit. It is presently disclosed that when ibrutinib is administered intraduodenally versus via the gastrointestinal tract in rats, the oral bioavailability of ibrutinib unexpectedly increased from 21 % to 100% as determined by AUC. This unexpected increase in oral bioavailability of ibrutinib can translate into a number of desirable practical benefits. The increase in oral bioavailability should enable administration of ibrutinib at a significantly lower therapeutically effective dose than is currently being used. The lower variability associated with this greater bioavailability should lead to a more reliable therapeutic response as well as more predictable drug absorption. And avoidance of exposure of Ibtrutinib to the stomach and/or use of lower therapeutically effective dose of ibrutinib can reduce or altogether eliminate potential adverse side effects of this drug such as diahrrea, nausea or emesis, and dizziness. U.S. Patent No. 7,514,444, mentioned above, discloses administration of 0.02-5000 mg/kg and1-1500 mg of ibrutinib/per day and in clinical trials 420 or 840 mg/day of ibrutinib is being administered to the patients with CLL and SLL. There is no reasonable expectation in the art that ibrutinib can be adminstered orally at lower efficacious doses to the patients with CLL and SLL, particularly as evidenced by the 420 or 840 mg/day of ibrutinib being administered in clinical trials to those patients. Moreover, other than for active agents that are unstable in the stomach or at acidic pH delivery of any active agent with low bioavailability further along in the gastrointestinal tract reduces the path length for drug absorption and would be expected to reduce bioavailability. Therefore, it was unexpected to achieve delivery of ibruntinib directly to the small intestine with greater bioavailability.

Accordingly, in one aspect, the present disclosure provides a solid oral dosage form comprising:

(i) ibrutinib and/or a pharmaceutically acceptable salt thereof;

(ii) means for release of ibrutinib in the intestine; and

(iii) at least one pharmaceutically acceptable excipient.

In one embodiment of above aspect, ibrutinib and/or a pharmaceutically acceptable salt thereof is released in the small intestine. In another embodiment, ibrutinib

and/or a pharmaceutically acceptable salt thereof is released to a region of the intestine in which the pH is about 5, or 5, or greater than 5. In another embodiment, said ibrutinib and/or a pharmaceutically acceptable salt thereof is released to a region of the intestine in which the pH is about 5.5, or greater than about pH 5.5. For example, the release is in one or more of the duodenum, jejunum, ileum, and colon. In one embodiment, the release is in one or more of the duodenum, jejunum, or ileum. In one embodiment, the release to the above regions of the intestine is achieved by coating ibrutinib and/or a pharmaceutically acceptable salt thereof or the dosage form containing ibrutinib and/or a pharmaceutically acceptable salt thereof with at least one coating chosen from enteric coatings and non-enteric time-delayed release coatings. In one embodiment, the release to the above regions of the intestine is achieved by coating ibrutinib and/or a pharmaceutically acceptable salt thereof or the dosage form containing ibrutinib and/or a pharmaceutically acceptable salt thereof with at least one coating chosen from enteric coatings. In one embodiment, the release to the above regions of the intestine is achieved by coating ibrutinib and/or a pharmaceutically acceptable salt thereof or the dosage form containing ibrutinib and/or a pharmaceutically acceptable salt thereof with at least one coating chosen from enteric coatings wherein the enteric coatings are chosen from polymeric coatings. In another embodiment, the enteric coating is is an anionic polymer such as polymethacrylates (e.g., methacrylic acid ethacrylate poly, methacrylic acid methyl methacrylate poly); cellulose-based polymers (e.g., cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), cellulose acetate succinate (CAS), hydroxypropylmethyl-cellulose phthalate (HPMCP), and hydroxypropylmethylcellulose acetate succinate (HPMCAS)) or polyvinyl derivatives such as polyvinyl acetate phthalate (PVAP).When a non-enteric coating is employed, the time-delayed release dosage forms are administered in fasted state and the time-delayed release coating is designed to erode, burst, or become hightly permeable in about 0.3 to about 3 hours or in about 0.5 to about 2 hours after administration to release ibrutinib and/or a pharmaceutically acceptable salt thereof.

In a second aspect, the present disclosure provides a solid oral dosage form comprising:

(i) ibrutinib and/or a pharmaceutically acceptable salt thereof;

(ii) means for increasing the oral bioavailability of ibrutinib, as measured by the area under the curve (AUC), as compared to when said ibrutinib and/or said pharmaceutically acceptable salt thereof are administered in an immediate release dosage form; and

(iii) at least one pharmaceutically acceptable excipient.

In one embodiment of the second aspect, the increase in the oral bioavailability of ibrutinib and/or a pharmaceutically acceptable salt thereof is due to the release of the

ibrutinib and/or a pharmaceutically acceptable salt thereof in the intestine. In another embodiment of the second aspect, the increase in the oral bioavailability of ibrutinib and/or a pharmaceutically acceptable salt thereof is due to the release of the ibrutinib and/or a pharmaceutically acceptable salt thereof in the small intestine. In another embodiment of the second aspect, ibrutinib and/or a pharmaceutically acceptable salt thereof is released in one or more of the duodenum, jejunum, or ileum. In one embodiment, the release to the above regions of the intestine is achieved by coating ibrutinib and/or a pharmaceutically acceptable salt thereof or a a dosage form containing ibrutinib and/or a pharmaceutically acceptable salt thereof with at least one coating chosen from enteric coatings and a non-enteric time-delayed release coatings. When the delayed release dosage forms are administered in fasted state, the time-delayed release coating is designed to erode, burst, or become very permeable in about 0.3 to about 3 hours or in about 0.5 to about 2 hours after administration to release ibrutinib and/or a pharmaceutically acceptable salt thereof. When the dosage form comprised of said compound is coated with a non-enteric coating, it is generally administered in the fasted state to avoid variability or delays in gastric emptying with meals and the resulting variability in the initiation of efficacious plasma levels.

In a third aspect, the present disclosure provides a solid oral dosage form comprising:

(i) ibrutinib and/or a pharmaceutically acceptable salt thereof;

(ii) at least one coating chosen from enteric coatings and non-enteric time-delayed release coatings; and

(ii) at least one pharmaceutically acceptable excipient.

In one embodiment, the said at least one coating is chosen from enteric coatings. In one embodiment,the said at least one coating is chosen from polymeric coatings. In one embodiment, the said at least one coating is chosen from enteric coatings where the enteric coating is a polymer which erodes to release ibrutinib and/or a pharmaceutically acceptable salt thereof at about pH 5 and above. In another embodiment, ibrutinib and/or a pharmaceutically acceptable salt thereof is released at about pH 5.5 and above or from about 5.5 to about 6.5. In yet another embodiment of the third aspect, ibrutinib and/or a pharmaceutically acceptable salt thereof is released in one or more of the duodenum, jejunum, or ileum. In one embodiment of the third aspect and embodiments contained therein the dosage form is coated. In one embodiment of the third aspect and embodiments contained therein said ibrutinib and/or said pharmaceutically acceptable salt thereof are coated.

In a fourth aspect, the present disclosure provides a solid oral dosage from comprising:

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