ANDA 211344

ANDA APPROVAL

Zydus Pharmaceuticals (USA) Inc.
U.S. Agent for Zydus Worldwide DMCC
73-B Route 31 North
Pennington, NJ 08534
Attention: Srinivas Gurram
Vice President and Head of RA and QA - North America

Dear Sir or Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on November 13, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Ibrutinib Capsules, 70 mg and 140 mg.

Reference is also made to the complete response letter issued by this office on August 31, 2020, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your Ibrutinib Capsules, 70 mg and 140 mg, to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Imbruvica Capsules, 70 mg and 140 mg, of Pharmacyclics LLC (Pharmacyclics).

The RLD upon which you have based your ANDA, Pharmacyclics's Imbruvica Capsules, 70 mg and 140 mg, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
7,514,444 (the '444 patent)	December 28, 2026
8,008,309 (the '309 patent)	November 13, 2027
8,476,284 (the '284 patent)	December 28, 2026
8,497,277 (the '277 patent)	December 28, 2026

8,563,563 (the '563 patent)	April 26, 2027
8,697,711 (the '711 patent)	December 28, 2026
8,703,780 (the '780 patent)	December 28, 2026
8,735,403 (the '403 patent)	December 28, 2026
8,754,090 (the '090 patent)	June 3, 2031
8,754,091 (the '091 patent)	December 28, 2026
8,952,015 (the '015 patent)	December 28, 2026
8,957,079 (the '079 patent)	December 28, 2026
8,999,999 (the '999 patent)	June 3, 2031
9,125,889 (the '889 patent)	June 3, 2031
9,181,257 (the '257 patent)	December 28, 2026
9,296,753 (the '753 patent)	October 30, 2033
9,540,382 (the '382 patent)	August 18, 2033
9,713,617 (the '617 patent)	June 3, 2033
9,725,455 (the '455 patent)	June 3, 2033
9,795,604 (the '604 patent)	October 24, 2034
9,801,881 (the '881 patent)	June 3, 2031
9,801,883 (the '883 patent)	June 3, 2031
9,814,721 (the '721 patent)	June 3, 2031
10,004,746 (the '746 patent)	June 3, 2031
10,016,435 (the '435 patent)	June 3, 2031
10,106,548 (the '548 patent)	June 3, 2033
10,125,140 (the '140 patent)	June 3, 2033

10,294,231 (the '231 patent)	June 3, 2033
10,294,232 (the '232 patent)	June 3, 2033
10,463,668 (the '668 patent)	October 24, 2034
10,478,439 (the '439 patent)	June 3, 2031
10,653,696 (the '696 patent)	June 3, 2031
10,695,350 (the '350 patent)	October 24, 2034
10,751,342 (the '342 patent)	June 3, 2031
10,752,634 (the '634 patent)	June 3, 2033 (140 mg strength only)

With respect to: 1) the '563, '780, '999, '889, '604, '881, '883, '721, '746, '435, '668, '350, and '342 patents; and 2) the '284, '277, '015, '382, and '439 patents (b) (4) (b) (4) your ANDA contains statements under section 505(j)(2)(A)(viii) of the FD&C Act that these are method-of-use patents that do not claim any indication or other conditions of use for which you are seeking approval under your ANDA.

With respect to: 1) the '444, '309, '711, '403, '090, '091, '079, '257, '753, '617, '455, '548, '140, '231, '232, '696, and '634 patents;[1] and 2) the '284, '277, '015, '382, and '439 patents (b) (4) (b) (4)[1] your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Ibrutinib Capsules, 70 mg and 140 mg, under this ANDA. You have notified the Agency that Zydus Worldwide DMCC (Zydus) complied with the requirements of section 505(j)(2)(B) of the FD&C Act. Litigation was initiated within the statutory 45-day period against Zydus for infringement of the '444, '309, '284, '277, '711, '403, '090, '091, '015, '079, '257, '753, '455, '548, and '140 patents in the United States District Court for the District of Delaware [Pharmacyclics LLC and Janssen Biotech, Inc. v. Zydus Worldwide DMCC, et al., Civil Action No. 18-00192 (consolidated)]. You have also notified the Agency that this case was dismissed.

With respect to Ibrutinib Capsules, 70 mg, we note that Zydus was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification for Ibrutinib Capsules, 70 mg. Therefore, with this approval, Zydus is eligible for 180 days of generic drug exclusivity for Ibrutinib Capsules, 70 mg. FDA notes that after issuance of this approval letter, eligibility for 180-day exclusivity is subject to future events that may result in forfeiture of exclusivity under section 505(j)(5)(D) of the FD&C Act. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the FD&C Act, will begin to run from the date of the commercial marketing identified in section

505(j)(5)(B)(iv). Please submit correspondence to this ANDA notifying the Agency within 30 days of the date of the first commercial marketing of this drug product or the RLD. If you do not notify the Agency within 30 days, the date of first commercial marketing will be deemed to be the date of the drug product's approval. See 21 CFR 314.107(c)(2).

With respect to Ibrutinib Capsules, 140 mg, we note that Zydus was one of the first ANDA applicants for Ibrutinib Capsules, 140 mg, to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, Zydus may be eligible for 180-days of shared generic drug exclusivity for Ibrutinib Capsules, 140 mg. This exclusivity, which is provided for under 505(j)(5)(B)(iv) of the FD&C Act, would begin to run from the date of the commercial marketing by any first applicant, as identified in section 505(j)(5)(B)(iv). The Agency notes that Zydus failed to obtain tentative approval of this ANDA within 30 months after the date of which the ANDA was filed. See section 505(j)(5)(D)(i)(IV) of the FD&C Act (forfeiture of exclusivity for failure to obtain tentative approval). The Agency is not, however, making a formal determination at this time of Zydus's eligibility for 180-day generic drug exclusivity. It will do so only if a subsequent paragraph IV applicant becomes eligible for full approval (a) within 180 days after any first applicant begins commercial marketing of Ibrutinib Capsules, 140 mg, or (b) at any time prior to the expiration of the '444, '309, '284, '277, '711, '403, '090, '091, '015, '079, '257, '753, '382, '617, and '455 patents if no first applicant has begun commercial marketing. Please submit correspondence to this ANDA notifying the Agency within 30 days of the date of the first commercial marketing of this drug product or the RLD. If you do not notify the Agency within 30 days, the date of first commercial marketing will be deemed to be the date of the drug product's approval. See 21 CFR 314.107(c)(2).

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: https://www.fda.gov/media/128163/download).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/opdp-form-fda-2253-and-request-advisory-comment-submissions.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[2] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such

violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at: http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at: https://www.fda.gov/media/71211/download. The SPL will be accessible via publicly available labeling repositories.

We remind you that you must continually monitor available labeling resources such as DRUGS@FDA for changes to your reference listed drug's labels and labeling and make any necessary revisions to your labels and labeling. More information on post-approval labeling changes may be found in the guidance for industry titled "Changes to an Approved NDA or ANDA" at: https://www.fda.gov/media/71846/download.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

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[1] With respect to the 140 mg strength product, the Agency notes that the '548, '140, '231, '232, '439, '696, and '634 patents were submitted to the Agency after submission of your ANDA. With respect to the 70 mg strength product, the Agency notes that the '231, '232, '439, and '696 patents were submitted to the Agency after submission of your ANDA. Litigation, if any, with respect to these patents would not create a statutory stay of approval.

[2] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

John Ibrahim

Digitally signed by John Ibrahim
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