ANDA 207486

ANDA TENTATIVE APPROVAL

Hikma Pharmaceuticals USA Inc.
U.S. Agent for Hikma Pharmaceuticals International Limited
1809 Wilson Road
Columbus, OH 43228
Attention: Jerald Andry
Senior Director, Drug Regulatory Affairs and Medical Affairs

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on June 18, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Everolimus Tablets, 2.5 mg, 5 mg, 7.5 mg, and 10 mg.

Reference is also made to the tentative approval letter issued by this office on December 16, 2016, the complete response letter issued by this office on February 25, 2019, 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 is safe and effective for use as recommended in the submitted labeling. The Office of Bioequivalence has determined your Everolimus Tablets, 2.5 mg, 5 mg, 7.5 mg, and 10 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Afinitor Tablets, 2.5 mg, 5 mg, 7.5 mg, and 10 mg, of Novartis Pharmaceutical Corporation (Novartis).

However, we are unable to grant final approval to your ANDA at this time because of the patent issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the Agency at this time (e.g., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention. This letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the FD&C Act.

The RLD upon which you have based your ANDA, Novartis's Afinitor Tablets, 2.5 mg, 5 mg, 7.5 mg, and 10 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
5,665,772 (the '772 patent)	March 9, 2020*
7,297,703 (the '703 patent)	June 6, 2020*

7,741,338 (the '338 patent)	December 6, 2019
8,410,131 (the '131 patent)	May 1, 2026*
8,436,010 (the '010 patent)	August 22, 2022*
8,778,962 (the '962 patent)	August 18, 2022*
9,006,224 (the '224 patent)	July 1, 2028

* with pediatric exclusivity added

With respect to the '010, '962, and '224 patents, 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 the '772, '703, '338, and '131 patents,[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 Everolimus Tablets, 2.5 mg, 5 mg, 7.5 mg, and 10 mg, under this ANDA. You have notified the Agency that Hikma Pharmaceuticals International Limited (Hikma) complied with the requirements of section 505(j)(2)(B) of the FD&C Act, and that litigation was initiated within the statutory 45-day period against Hikma for infringement of the '772, '703, and '338 patents in the United States District Court for the District of Delaware [Novartis Pharmaceuticals Corporation and Novartis AG v. West-Ward Pharmaceuticals International Limited, Civil Action Nos. 14-01508 and 15-00128]. You have notified the Agency that these cases were dismissed.

You have also notified the Agency that litigation was initiated within the statutory 45-day period against Hikma for infringement of the '131 patent in the United States District Court for the District of Delaware [Novartis Pharmaceuticals Corporation and Novartis AG v. West-Ward Pharmaceuticals International Limited, Civil Action No. 15-00474]. On December 21, 2017, the court ordered that pursuant to 35 U.S.C. 271(e)(4)(A), "the effective date under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) of any final approval by the United States Food and Drug Administration of Defendant's ANDA No. 207486 for the Everolimus RCC Indication shall be a date not earlier than the expiration of the pediatric exclusivity for the '131 patent, which is May 1, 2026; except to the extent subsequently (a) agreed between Plaintiffs and Defendant or (b) ordered or otherwise permitted by this Court or other tribunal."[2] You have further notified the Agency that, on May 13, 2019, the United States Court of Appeals for the Federal Circuit affirmed the decision of the district court. Therefore, final approval of your ANDA cannot be granted until the '131 patent has expired, currently May 1, 2026, as specified in the court order.

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.

RESUBMISSION

To request final approval, please submit an amendment titled "FINAL APPROVAL REQUESTED" with enough time to permit FDA review prior to the date you believe that your ANDA will be eligible for final approval. A request for final approval that contains no new data, information, or other changes to the ANDA generally requires a period of 90 days for Agency review. Accordingly, such a request for final approval should be submitted no later than 90 days prior to the date on which you seek approval. A request for final approval that contains substantive changes to this ANDA or changes in the status of the manufacturing and testing facilities' compliance with cGMPs will be classified and reviewed according to OGD policy in effect at the time of receipt. Applicants should review available agency guidance for industry related to amendments under the generic drug user fee program to determine the duration of Agency review needed to review the changes submitted. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

The amendment requesting final approval should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, settlement or licensing agreement, or other information described in 21 CFR 314.107, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, e.g., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a "FINAL APPROVAL REQUESTED."

In addition to the amendment requested above, the Agency may request, at any time prior to the date of final approval, that you submit an additional amendment containing information as specified by the Agency. Failure to submit either or, if requested, both types of amendments described above may result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the FD&C Act. Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under section 505(j) of the FD&C Act, and will not be listed in the Orange Book. Should you believe that there are grounds for issuing the final approval letter prior to May 1, 2026,[3] you should amend your ANDA accordingly.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[4] 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 (FDFs) or active pharmaceutical ingredients (APIs) 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.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

For further information on the status of this ANDA or upon submitting an amendment to the ANDA, please contact Emmanuel Kerry, Regulatory Project Manager, at (301) 796 - 7737.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, PharmD
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

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[1] With respect to the 10 mg strength, the Agency notes that the '338 patent was submitted to the Agency after submission of your ANDA. Litigation, if any, with respect to this patent would not create a statutory stay of approval.

[2] Final Judgment, *Novartis Pharmaceuticals Corporation and Novartis AG v. West-Ward Pharmaceuticals International Limited*, Civil Action No. 15-00474 (Dec. 21, 2017), at 3-4.

[3] We note that this ANDA currently is eligible for approval the day after expiration of the pediatric exclusivity period. See Section 505A(b)(1)(B) of the FD&C Act. If this day falls on a Saturday, Sunday, or Federal holiday, it will be eligible for approval the next business day.

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

Heidi Lee

Digitally signed by Heidi Lee
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