



ANDA 211000

ANDA TENTATIVE APPROVAL

Amneal Pharmaceuticals of New York, LLC
U.S. Agent for Amneal EU, Limited
Attention: Janie M. Gwinn
Vice President, Regulatory Affairs

Dear Janie M. Gwinn:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on October 18, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Macitentan Tablets, 10 mg.

Reference is also made to the complete response letter issued by this office on August 16, 2018, 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. We have determined your Macitentan Tablets, 10 mg to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Opsumit Tablets, 10 mg, of Actelion Pharmaceuticals US, Inc. (Actelion) NDA - 204410.

However, we are unable to grant final approval to your ANDA at this time because of the exclusivity 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.

The reference listed drug (RLD) upon which you have based your ANDA, Actelion's Opsumit Tablets, 10 mg, is subject to periods of patent protection. The following patents and expiration dates (with pediatric exclusivity added) are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
7,094,781 (the '781 patent)	June 5, 2026
8,268,847 (the '847 patent)	October 18, 2029

8,367,685 (the '685 patent)	April 4, 2029
9,265,762 (the '762 patent)	November 29, 2027
10,946,015 (the '015 patent)	March 11, 2027

Your ANDA contains paragraph IV certifications to the '847, '685, '762, and '015 patents 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 Macitentan Tablets, 10 mg, under this ANDA. You have notified the Agency that Amneal EU, Limited (Amneal) complied with the requirements of section 505(j)(2)(B) of the FD&C Act, and that no action for infringement of the '847, '685, '762 patents was brought against Amneal within the statutory 45-day period.

The RLD upon which you have based your ANDA, Actelion's Opsumit Tablets, 10 mg, is subject to periods of exclusivity. As noted above, the pediatric exclusivity period associated with the '781 patent is scheduled to expire on June 5, 2026.² Therefore, final approval cannot be granted until expiration of the pediatric exclusivity period associated with the '781 patent. See section 505A(b)(1)(B)(i) of the FD&C Act.²¹

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a) of the FD&C Act]. In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) is subject to certain elements of the REMS required for the applicable listed drug.

In our letter dated December 1, 2017, we notified you that a REMS is required for macitentan-containing products to ensure that the benefits of the drug outweigh the risk of embryo-fetal toxicity. We indicated that your REMS must include elements to assure safe use and an implementation system.

We have determined that, at this time, a REMS is no longer necessary for macitentan-containing products, to ensure that its benefits outweigh its risks. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

REQUIREMENTS AND RECOMMENDATIONS POST APPROVAL

Under applicable statutes, regulations, and guidances, if your ANDA receives final approval, it may be subject to certain requirements and recommendations post approval, including requirements regarding changes to approved ANDAs, postmarketing reporting, promotional materials, and annual facility fees, among others. For information

on post-approval requirements and recommendations for ANDAs and a list of resources for ANDA holders, we refer you to <https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/requirements-and-resources-approved-andas>.

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 3 months for Agency review. Accordingly, such a request for final approval should be submitted no later than 3 months 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. As part of this consideration, applicants should monitor any changes to the RLD that occur after tentative approval, including changes in labeling, patent or exclusivity information, or marketing status. 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.

For further information on the status of this ANDA or upon submitting an amendment to the ANDA, please contact Kimberly McCullough, Regulatory Project Manager, at (240) 402 - 9021.

Sincerely yours,

{See appended electronic signature page}

For Kendra S. Stewart, R.Ph., Pharm.D.
CAPT, United States Public Health Service
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

¹ Although your ANDA previously contained a paragraph IV certification to the '781 patent, upon expiration of that patent on December 5, 2025, your certification to the '781 patent is deemed to be a paragraph II certification.

² 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.



Paul
Levine

Digitally signed by Paul Levine

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