ANDA 211128

ANDA APPROVAL

Syneos Health, LLC
U.S. Agent for Alembic Pharmaceuticals Limited
Attention: Shawna Richards
Manager

Dear Shawna Richards:

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 tentative approval letter issued by this office on March 11, 2022, 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 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.

The 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 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
7,094,781 (the '781 patent)	December 5, 2025
8,268,847 (the '847 patent)	April 18, 2029
8,367,685 (the '685 patent)	October 4, 2028
9,265,762 (the '762 patent)	May 29, 2027
10,946,015 (the '015 patent)	September 11, 2026

Your ANDA contains paragraph IV certifications to the '781, '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 Alembic

Pharmaceuticals Limited (Alembic) 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 Alembic for infringement of the '781 patent in the United States District Court for the District of New Jersey [Actelion Pharmaceuticals US, Inc. and Actelion Pharmaceuticals Ltd. v. Alembic Pharmaceuticals Limited and Alembic Pharmaceuticals, Inc., Civil Action No. 23-01902]. You have also notified the Agency that this case was dismissed.

With respect to the '847 patent, your ANDA contains a statement under section 505(j)(2)(A)(viii) of the FD&C Act that this is a method-of-use patent that does not claim any indication or other conditions of use for which you are seeking approval under your ANDA.

With respect to 180-day generic drug exclusivity, we note that Alembic was one of the first ANDA applicants for Macitentan Tablets, 10 mg, to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, Alembic may be eligible for 180 days of shared generic drug exclusivity for Macitentan Tablets, 10 mg. The Agency notes that Alembic failed to obtain tentative approval of its ANDA within 30 months after the date on 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 Alembic's eligibility for 180-day generic drug exclusivity.

At least one first applicant remains eligible for 180-day generic drug exclusivity for Macitentan Tablets, 10 mg absent forfeiture under section 505(j)(5)(D) of the FD&C Act.[1] This exclusivity, which is provided for under section 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). 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).

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 acknowledge receipt of your submission dated July 1, 2022, of a proposed REMS. 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.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standard for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website as https://www.uspnf.com/.

REQUIREMENTS AND RECOMMENDATIONS POST APPROVAL

Under applicable statutes, regulations, and guidances, your ANDA 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.

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] See also draft guidance for industry on 180-Day Exclusivity: Questions and Answers, Q. 42, at 26 (Jan. 2017).

Catherine Poole

Digitally signed by Catherine Poole
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