



ANDA 211195

ANDA APPROVAL

Apotex, Corp.
U.S. Agent for Apotex, Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Kiran Krishnan:

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 September 1, 2021, 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).

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>U.S. Patent Number</u>	<u>Expiration Date</u>
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,¹ 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 Apotex, Inc. (Apotex) 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 Apotex for infringement of the '781 patent in the United States District Court for the District of Delaware [Actelion Pharmaceuticals US, Inc. and Actelion Pharmaceuticals, Ltd. v. Apotex, Inc. and Apotex, Corp., Civil Action No. 23-00734]. 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 Apotex was one of the first ANDA applicants to submit a substantially complete ANDA with a paragraph IV certification for Macitentan Tablets, 10 mg. Therefore, with this approval, Apotex may be eligible for 180 days of shared generic drug exclusivity for Macitentan Tablets, 10 mg. The Agency notes that Apotex 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 Apotex'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. 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.

The details of the REMS requirements were outlined in our REMS notification letter dated December 1, 2017.

Your final proposed REMS, referenced in Drug Master File (DMF) (b) (4), is approved, and will be posted on the FDA REMS website: <http://www.fda.gov/remis>. Other products may be added in the future if additional NDAs or ANDAs are approved.

The Macitentan REMS consists of Elements to Assure Safe Use (ETASU) and an implementation system.

Your REMS must be fully operational before you introduce Macitentan into interstate commerce.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

We remind you that you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act.

We also remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application from using any element to assure safe use to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing a REMS assessment or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**ANDA 211195 REMS ASSESSMENT
CROSS REFERENCE TO THE REMS DMF**

or

**NEW SUPPLEMENT FOR ANDA 211195/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION
CROSS REFERENCE TO THE REMS DMF**

or

**NEW SUPPLEMENT FOR ANDA 211195/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION
CROSS REFERENCE TO THE REMS DMF**

or

**NEW SUPPLEMENT FOR ANDA 211195/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING
CHANGES SUBMITTED IN SUPPLEMENT XXX
CROSS REFERENCE TO THE REMS DMF**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

**REMS REVISION FOR ANDA 211195
CROSS REFERENCE TO THE REMS DMF**

The Macitentan REMS uses a Type V DMF for shared system REMS submissions. Please refer to the draft guidance for industry *Use of a Drug Master File for Shared System REMS Submissions*,² for instructions on how to submit and reference the shared system REMS DMF.

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

¹ The Agency notes that the '015 patents 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 We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.



John
Ibrahim

Digitally signed by John Ibrahim

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