ANDA 208043

ANDA TENTATIVE APPROVAL

Actavis Laboratories FL, Inc.
2945 West Corporate Lakes Blvd.
Suite B
Weston, FL 33331
Attention: Alberto Rivalta
Senior Director, Regulatory Affairs

Dear Alberto Rivalta:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on March 12, 2015, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Naltrexone Hydrochloride and Bupropion Hydrochloride Extended-Release Tablets, 8 mg/90 mg.

Reference is also made to the complete response letter issued by this office on January 25, 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. We have determined your Naltrexone Hydrochloride and Bupropion Hydrochloride Extended-Release Tablets, 8 mg/90 mg, to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Contrave Tablets, 8 mg/90 mg of Nalpropion Pharmaceuticals, LLC (Nalpropion).

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, Nalpropion's Contrave Tablets, 8 mg/90 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
7,375,111 (the '111 patent)	March 26, 2025
7,462,626 (the '626 patent)	July 20, 2024
8,088,786 (the '786 patent)	February 3, 2029
8,318,788 (the '788 patent)	November 8, 2027
8,722,085 (the '085 patent)	November 8, 2027
8,815,889 (the '889 patent)	July 20, 2024
8,916,195 (the '195 patent)	February 2, 2030
9,107,837 (the '837 patent)	June 4, 2027
9,125,868 (the '868 patent)	November 8, 2027
9,248,123 (the '123 patent)	January 13, 2032
9,633,575 (the '575 patent)	June 25, 2033
10,231,964 (the '964 patent)	July 2, 2034
10,307,376 (the '376 patent)	November 8, 2027
10,403,170 (the '170 patent)	June 5, 2033
10,828,294 (the '294 patent)	July 2, 2034
10,835,527 (the '527 patent)	July 2, 2034
11,033,543 (the '543 patent)	January 10, 2031
11,139,056 (the '056 patent)	June 5, 2033
11,278,544 (the '544 patent)	April 21, 2024
11,324,741 (the '741 patent)	May 29, 2029

With respect to the '575, '964, '376, '170, '294, '527, '543, '056, '544, and '741 patents, your ANDA contains paragraph III certifications to each of the patents under section 505(j)(2)(A)(vii)(III) of the FD&C Act stating that Actavis Laboratories FL, Inc. (Actavis) will not market Naltrexone Hydrochloride and Bupropion Hydrochloride Extended-

Release Tablets, 8 mg/90 mg, prior to the expiration of the patents. Therefore, final approval of your ANDA may not be granted pursuant to section 505(j)(5)(B)(ii) of the FD&C Act until the '964, '294, and '527patents have expired, currently July 2, 2034.

Your ANDA contains paragraph IV certifications to the '111, '626, '786, '788, '085, '889, '195, '837, and '123 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 Naltrexone Hydrochloride and Bupropion Hydrochloride Extended-Release Tablets, 8 mg/90 mg, under this ANDA. You have notified the Agency that Actavis 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 Actavis for infringement of the '111, '626, '786, '788, '085, '889, and '195 patents in the United States District Court for the District of Delaware, [Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals International GmbH, Takeda Pharmaceuticals USA, Inc., Takeda Pharmaceuticals America, Inc., and Orexigen Therapeutics, Inc. v. Actavis Laboratories FL, Inc., Andrx Corporation, Actavis Pharma, Inc., and Actavis, Inc. Civil Action No. 15-451]. You have also notified the Agency that the district court issued an opinion on October 13, 2017, stating, among other things, that "Plaintiff proved . . . that Defendant directly infringes . . . [the asserted claim] of the '195 patent" and that "Defendants failed to prove . . . [that the asserted claim] of the '195 patent [is] invalid."[2] You have also notified the Agency that on December 23, 2019, the United States Court of Appeals for the Federal Circuit entered a mandate in accordance with the court's judgment entered August 15, 2019, affirming the district court's decision with regard to the '195 patent.[3] Therefore, final approval cannot be granted until the '195 patent has expired, currently February 2, 2030.

With respect to the '868 patent, the Agency has determined that information on this patent was submitted to the Agency by the new drug application (NDA) holder (a) after the date of the submission of your ANDA, and (b) more than 30 days after the patent was required to be submitted under 21 CFR 314.53. Therefore, under 21 CFR 314.94(a)(12)(vi), no person with an appropriate patent certification at the time of the submission of the patent was required to submit an amended patent certification to address the '868 patent. You elected not to submit an amended patent certification with respect to this patent.

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 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. Should you believe that there are grounds for issuing the final approval letter prior to July 2, 2034, 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 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.

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.

For further information on the status of this ANDA or upon submitting an amendment to the ANDA, please contact LCDR Brandy Sims, Regulatory Project Manager, at (240) 402 - 4255.

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] The Agency notes that the '837 and '123 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] Orexigen Therapeutics, Inc. v. Actavais Laboratories FL, Inc., Case No. 15-cv-00451, Dkt. 184 (D. Del. Oct. 13, 2017).

[3] Nalpropion Pharmaceuticals LLC v. Actavis Laboratories FL, Inc., Case 18-1221, Dkt. 114 (Fed. Cir. Dec. 23, 2019).

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

Catherine Poole

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