ANDA 204982

ANDA APPROVAL

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

Dear Alberto Rivalta:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on July 18, 2013, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Phentermine and Topiramate Extended-Release Capsules, 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg and 15 mg/92 mg.

Reference is also made to the complete response letter issued by this office on October 12, 2023, 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 Phentermine and Topiramate Extended-Release Capsules, 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg and 15 mg/92 mg, to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Qsymia Extended-Release Capsules, 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg and 15 mg/92 mg of Vivus LLC (Vivus).

The RLD upon which you have based your ANDA, Vivus's Qsymia Extended-Release Capsules, 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg and 15 mg/92 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
8,580,298 (the '298 patent)	May 15, 2029
8,580,299 (the '299 patent)	June 14, 2029
8,895,057 (the '057 patent)	June 9, 2028
8,895,058 (the '058 patent)	June 9, 2028

9,011,905 (the '905 patent)	June 9, 2028
9,011,906 (the '906 patent)	June 9, 2028

Your ANDA contains paragraph IV certifications to each of the 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 Phentermine and Topiramate Extended-Release Capsules, 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg and 15 mg/92 mg, under this ANDA. You have notified the Agency that Actavis Laboratories FL, Inc. (Actavis) complied with the requirements of section 505(j)(2)(B) of the FD&C Act.

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) of the FD&C Act 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 September 17, 2014.

Your final proposed REMS, received on May 15, 2024, is approved, and will be posted on the FDA REMS website: http://www.fda.gov/rems. Other products may be added in the future if additional NDAs or ANDAs are approved.

The Phentermine and Topiramate Extended-Release Capsules REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), and an implementation system.

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

Your REMS, known as the Phentermine and Topiramate Extended-Release Capsules REMS, is approved as a separate REMS from that of the reference listed drug, using a different, comparable aspect of the ETASU. Pursuant to section 505-1(i)(3) of the FD&C Act, FDA is requiring that this REMS can be used with respect to any other drug that is the subject of an application under section 505(j) or 505(b) of the FD&C Act that references the same listed drug.

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.

FDA has determined that assessments are needed for the Phentermine and Topiramate Extended-Release Capsules REMS.

Additionally, the details for what should be included in your REMS assessments and the dates of the REMS assessments are listed in Appendix 1.

i. If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches, other analysis plans and assessment approaches used to assess a REMS be submitted for FDA review as follows: Submit your proposed audit plan and non-compliance plan for FDA review within 60 days of this letter.

ii. Submit your proposed protocol for the knowledge survey(s) for FDA review within 90 days of this letter.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **ANDA 204982 REQUEST FOR REMS ASSESSMENT METHODOLOGY PROTOCOL REVIEW**
> (insert concise description of content in bold capital letters, e.g.,
> **SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)**

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) of the FD&C Act 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 204982 REMS ASSESSMENT**

or

NEW SUPPLEMENT FOR ANDA 204982/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 204982/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 204982/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

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 204982

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Do not submit the SPL formatted REMS to your application. Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling.*

For additional information on submitting REMS in SPL format, please email REMSWebsite@fda.hhs.gov.

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

Enclosure:

REMS

[1] The Agency notes that the '298, '299, '057, '058, '905 and '906 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.

Appendix 1

Phentermine and Topiramate Extended-Release Capsules REMS Assessment Plan

REMS Assessments are due to be submitted to the FDA at 12 months following the approval of the REMS and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. The Phentermine and Topiramate Extended-Release Capsules REMS Applicant(s) will submit each REMS assessment(s) so that it will be received by the FDA on or before the due date.

The Phentermine and Topiramate Extended-Release Capsules REMS assessment plan must include, but is not limited to, the following:

For each metric, provide the two previous, current, and cumulative reporting periods (if applicable), unless otherwise noted.

REMS Implementation and Operations

1. **Program Implementation (for the first assessment only)**
   a. Phentermine and Topiramate Extended-Release Capsules REMS Launch Date.
   b. Date when Phentermine and Topiramate Extended-Release Capsules REMS materials became available on the **REMS Website** and via the REMS Coordinating Center.
   c. The dates stakeholders can enroll online, by mail, or by fax.

2. **REMS Certification and Enrollment Statistics**

   a. Pharmacies
      i. Number of certified pharmacies stratified by pharmacy type (i.e., mail order, chain, independent)
      ii. Number and percentage of newly certified pharmacies stratified by pharmacy type (i.e., mail order, chain, independent)
      iii. Number and percentage of active certified pharmacies (i.e., have dispensed phentermine and topiramate extended-release capsules within the reporting period) stratified by pharmacy type (i.e., mail order, chain, independent)
   b. Wholesalers-Distributors
      i. Number of authorized wholesalers-distributors.
      ii. Number and percentage of newly authorized wholesalers-distributors.
      iii. Number and percentage of active authorized wholesalers-distributors (i.e., have shipped phentermine and topiramate extended-release capsules within the reporting period).

3. **REMS Utilization Data**
   a. Patient Demographics
      i. Unique number of all patients who received phentermine and topiramate extended-release capsules stratified by gender.
      ii. Unique number of patients of reproductive potential receiving phentermine and topiramate extended-release capsules stratified by the following age ranges (years):
         1. 12 - < 18
         2. 18 - < 25
         3. 25 - < 45
         4. 45 - < 53
         5. 53+
      iii. Average duration of phentermine and topiramate extended-release capsules treatment among patients of reproductive potential based on patient age outlined above.
   b. Prescription data
      i. Provide a table that includes the following for the overall population and another table for patients of reproductive potential based on patient age as outlined above:
         1. Total number of unique patients.
         2. Number and percentage of total prescriptions dispensed.
         3. Number and percentage of total prescriptions dispensed for new prescriptions and refill(s)
         4. Number and percentage of total prescriptions dispensed by dosage strength.

4. **REMS Infrastructure and Performance**
   a. REMS Coordinating Center
      i. Number of contacts by stakeholder type (i.e., pharmacies, wholesalers-distributors, other)
      ii. Summary of reasons for calls (e.g., enrollment question, location of a pharmacy) and by reporter (Authorized Representative, pharmacy, other)
      iii. Summary of frequently asked questions (FAQ) by stakeholder type
      iv. Summary report of REMS-related problems identified and resulting corrective actions.
      v. Provide an assessment for any reports to the REMS Coordinating Center indicating a burden to the healthcare system or barrier(s) to patient access. Include in the assessment whether the burden or access issue is attributable to the REMS, insurance, healthcare availability, or other issues.
   b. REMS Website
      i. Number of visits and unique visits to the **REMS Website**
      ii. Number of REMS materials downloaded for each material.

5. **REMS Compliance**
   a. Audits

i. Provide a report of audit findings for each stakeholder including but not limited to:
   1. A copy of the audit plan for each stakeholder
   2. Number of audits expected and performed.
   3. The number and type of deficiencies (e.g., critical, major, or minor findings) noted for audited stakeholders.
   4. For those with deficiencies noted, report the number that successfully completed a corrective and preventative action (CAPA) plan within the timeline specified in the audit plan.
   5. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken.
   6. Use a unique identifier (ID) for stakeholders that had deviations to track deviations by stakeholders over time.
   7. Confirm documentation of completion of training for relevant staff
   8. Verify the existence of documented processes and procedures for complying with the REMS.
   9. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed.

b. Noncompliance
   i. Provide a summary of the noncompliance identified, including but not limited to:
      1. A copy of the Noncompliance Plan which addresses the criteria for noncompliance for each stakeholder, actions taken to address noncompliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS.
      2. Summary of noncompliance events identified per pharmacy and wholesalers-distributors including any CAPAs and status of corrective actions.
      3. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:
         a. The unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time.
         b. The source of the noncompliance data.
         c. The results of the root cause analysis.
         d. What action(s) were taken in response and whether any follow-up is planned.
      4. Number and type of pharmacy decertified and the reason for decertification.
      5. Summary of annual compliance reports provided to the Phentermine and Topiramate Extended-Release Capsules REMS Applicant(s) by corporate chains, mail order pharmacies, and contracted wholesalers-distributors.

6. **Report on the periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21CFR 208.24 and the Patient Brochure**

    a. Pharmacist Materials Distribution
        i. Assessment of pharmacists' compliance with the REMS dispensing requirements, specifically the provision of a **Medication Guide** and the **Patient Brochure**

Health Outcomes and/or Surrogate of Health Outcomes

7. **Safety Surveillance**
    a. A summary of pregnancy cases including the following information:
        i. Event identification number.
        ii. Source of the report.
        iii. Contraceptive methods used.
        iv. Pregnancy outcome.
        v. Age of patient.
        vi. Cases of congenital malformations for each exposed pregnancy.
    b. Follow-up of outstanding pregnancy reports from the previous assessment reporting period.
    c. Root cause analysis of each reported pregnancy to determine the reason the REMS failed to prevent the pregnancy exposure. This root cause analysis should include patient interviews as a component. Include the protocol utilized to conduct this root cause analysis.
    d. Overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication.

Knowledge

8. **Evaluation of Knowledge of the Phentermine and Topiramate Extended-Release Capsules REMS and Risks of Phentermine and Topiramate**
    a. An assessment of patients of reproductive potentials' understanding of:
        i. The increased risk of embryo-fetal toxicity with major congenital malformations, including but not limited to cleft lip and/or cleft palate (oral clefts), and of being small for gestational age (SGA) in a fetus exposed to phentermine and topiramate extended-release capsules during the first trimester of pregnancy.
        ii. The importance of pregnancy prevention for patients of reproductive potential receiving phentermine and topiramate extended-release capsule therapy.
        iii. The need to promptly discontinue phentermine and topiramate extended-release capsule therapy in the event of a pregnancy.
        iv. The receipt, reading and understanding by patients of reproductive potential of the Phentermine and Topiramate Extended-Release Capsules **Medication Guide** and the **Patient Brochure**
        v. Patients of reproductive potential's receipt of counseling about pregnancy prevention and effective contraceptive use, including:

1. Counseling provider (i.e., prescriber, office nurse, pharmacist)
2. Duration of time spent counseling.
3. Frequency of patient counseling (each visit while receiving phentermine and topiramate extended-release capsules; first time prescribed phentermine and topiramate extended-release capsules)

b. An assessment of pharmacists' understanding of:
   i. The increased risk of embryo-fetal toxicity with major congenital malformations, including but not limited to cleft lip and/or cleft palate (oral clefts), and of being small for gestational age (SGA) in a fetus exposed to phentermine and topiramate extended-release capsules during the first trimester of pregnancy.
   ii. The importance of pregnancy prevention for patients of reproductive potential receiving phentermine and topiramate extended-release capsules.
   iii. The need to promptly discontinue phentermine and topiramate extended-release capsule therapy in the event of a pregnancy.
   iv. Assessment of pharmacists' awareness and understanding of the need to provide a **Medication Guide** and the **Patient Brochure** with every prescription dispensed.

9. The requirements for assessments for an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

Paul
Levine

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