CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205489Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205489

COMPLETE RESPONSE

Neos Therapeutics, Inc.
Attention: Dorothy J. Engelking
Vice President, Regulatory Affairs
2940 N. HWY 360, Suite 400
Grand Prairie, TX 75050

Dear Ms. Engelking:

Please refer to your New Drug Application (NDA) dated and received on January 9, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Cotempla XR-ODT (Methylphenidate Extended-Release Orally Disintegrating) 10 mg, 20 mg, and 30 mg tablets.

We acknowledge receipt of your amendments dated January 16, 2015, January 20, 2015, January 28, 2015, February 10, 2015, February 16, 2015, February 27, 2015, March 6, 2015, March 17, 2015, March 19, 2015, April 6, 2015, April 10, 2015, April 20, 2015, April 21, 2015, July 14, 2015, July 16, 2015, July 20, 2015, August 4, 2015, August 7, 2015, August 20, 2015, September 1, 2015, September 4, 201, and September 25, 2015.

We also acknowledge receipt of your amendment dated September 25, 2015, regarding the carton/container labels, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

This new drug application provides for the use of Cotempla XR-ODT (Methylphenidate Extended-Release Orally Disintegrating) tablets for the treatment of Attention Deficit Hyperactive Disorder (ADHD).

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

DEFICIENCIES WHICH PRECLUDE APPROVAL

Office of Pharmaceutical Quality (OPQ):

1. You must bridge the clinical and to-be-marketed drug product formulations with a bioequivalence study. The to-be-marketed drug product will have (b) (4)% (b) (4) (w/w) delayed-release and (b) (4)% (b) (4) extended-release (b) (4) than the clinical batches. The provided dissolution data not be used to support this change. Changes of this extent,

especially to the extended-release [redacted], require bioequivalence studies to establish the bridge between the two formulations. The specifics of these studies are listed under the "Office of Clinical Pharmacology" section below.

2. You must establish, validate and fully justify an unequivocal commercial [redacted] operation and control—your description of this process in communications during the review cycle contradicts that described in the application. You state in 3.2.P.2.3 that the commercial scale process will use [redacted] but state in the 20 AUG 2015 amendment [redacted]

Office of Clinical Pharmacology (OCP):

1. As stated in the product quality section above, an adequate bridge between the clinical trial formulation (Lot: 2E116E) and the to-be-marketed formulation has not been established. Due to this lack of an adequate bridge, the findings from the efficacy and safety trial (NT0102.1004) based on the clinical trial formulation may not inform the safety and effectiveness of the to-be marketed product.

2. An adequate bridge has not been established between the to-be-marketed formulation, and the listed drug (Metadate CD). Thus, the Agency's finding of efficacy and safety for Metadate CD may not be used to support the approval of the to-be marketed product until a bridge is established.

3. Pediatric pharmacokinetic information obtained with the clinical pharmacology formulation (Lot: 1E101A) is insufficient to support extrapolation of efficacy findings (based on clinical trial formulation) from children into adolescents [redacted] for the to-be marketed formulation.

4. Food effect findings based on the clinical pharmacology formulation (Lot: 1E101A) may not inform the food effect on the to-be-marketed formulation. The to-be-marketed formulation contains the [redacted] amount of release-controlling [redacted] among the three formulations. Because the level of interaction between food and the release controlling [redacted] is unclear, it may not be appropriate to extrapolate the food effect findings from the clinical pharmacology formulation to the to-be-marketed formulation.

Based on the Office of Clinical Pharmacology's assessment, the following remedy actions are necessary.

- The sponsor should conduct a bioequivalence study to bridge the to-be-marketed formulation with the clinical trial formulation (Lot: 2E116E) under fasted condition.

- Food effect on the to-be-marketed formulation should be assessed. It can be evaluated by adding one more arm (i.e., to-be-marketed formulation in fed state) in the above bioequivalence study.

OTHER DEFICIENCIES/COMMENTS

Office of Pharmaceutical Quality (OPQ):

1. Change the dosage strengths so that they reflect methylphenidate base content. This will be in accordance with the USP <1121> salt policy and Agency salt naming guidance. The proposed dosage strength is based on methylphenidate hydrochloride. However, the drug product does not contain methylphenidate hydrochloride.

2. The drug substance is (b) (4). Provide justification for the use of (b) (4).

3. (b) (4)

4.

5. The amount of extended- and delayed-release (b) (4) in the final drug product formulation will vary. Provide the acceptable extended- and delayed-release (b) (4) range for the final drug product formulation. Provide justification demonstrating that the permitted range does not impact drug product quality and efficacy.

6. Provide a table indicating the composition of the to-be marketed drug product formulation. Ensure the table has the following information:
   a. The targeted drug product composition (mg and w/w%)
   b. The minimum acceptable amount of each excipient [(b) (4)], sucralose, triethyl [(b) (4)], ethylcellulose, methacrylic acid [(b) (4)]) for a drug product composition (mg and w/w%)
   c. The maximum acceptable amount of each excipient [(b) (4)], sucralose, triethyl [(b) (4)], ethylcellulose, methacrylic acid [(b) (4)]) for a drug product composition (mg and w/w%)

7. Provide a table with the drug product composition of each drug product batch manufactured including previous and newly prepared batches. Indicate which batches were used in clinical trials. Ensure the information is accurate and consistent as there were multiple discrepancies in previously provided data.

8. Provide release and three months' accelerated and long-term stability data from three batches manufactured using the commercial manufacturing process. Ensure the newly manufactured batches have the same drug product formulation as the batches used in the BE study.

9. You indicate that the polystyrene sulfonate specification contains a [(b) (4)] specification matching the manufacturer's requirements. Provide justification for choosing this [(b) (4)] [(b) (4)] acceptance criterion.

10. We note that the application included inconsistent information on critical issues, for example, information used to support the differences in the clinical and the to-be-marketed formulations, including differences in excipient level for the clinical batches. The application also contained contradictory statements such as on whether [(b) (4)] [(b) (4)]. These inconsistencies make definitive formulation comparisons between the clinical and to-be-marketed batches impossible.

11. Be advised that [(b) (4)] This is because of the significant difference between the formulations and the fact that it comprises [(b) (4)]% of tablet weight.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of

labeling [21 CFR314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Please refer to correspondence dated, April 20, 2015 which addresses the proposed proprietary name, Cotempla XR-ODT. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65 You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please call CAPT Bill Bender, Senior Regulatory Project Manager, at (301) 796-2145 or via email at william.bender@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
11/06/2015