APPLICATION NUMBER:

207145Orig1s000

OTHER ACTION LETTERS
NDA 207145

Newron Pharmaceuticals US, Inc.
Attention: Richard Vogel, PhD
89 Headquarters Plaza North, Suite 1438
Morristown, NJ 07960

Dear Dr. Vogel:

Please refer to your New Drug Application (NDA) dated December 29, 2014, received December 29, 2014, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xadago (safinamide) 50 mg and 100 mg Tablets.

We acknowledge receipt of your major amendment dated August 31, 2015, which extended the goal date by three months.

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.

CONTROLED SUBSTANCE COMMENTS

1. Your nonclinical drug discrimination study (Study RS1414) that used amphetamine as the training drug indicates that the interoceptive cues (internal sensations) produced by safinamide are weakly similar to those induced by amphetamine. That study, however was designed only to assess whether safinamide produces effects similar to those produced by a stimulant. Since safinamide has sedative effects, a discrimination study using a sedative/depressant is necessary to further characterize safinamide abuse potential. We are aware that you are conducting a study assessing the interoceptive cues of safinamide in comparison to midazolam, a sedative drug, (Study RS1426), but that study has not been submitted to the NDA during this review cycle.

2. Your nonclinical self-administration study (Study RS1417) has significant design problems, which limit its interpretability:

   a. Inappropriate positive control (positive control was not a CNS depressant)
   b. The fixed ratio schedule (FR-30) in which subjects were required to respond (lever press) 30 times for each IV drug infusion, was too high for a drug with sedative effects.
   c. No randomization to treatment
d. Small number of subjects (4 primates)
e. The tested doses did not produce peak exposure levels comparable to those seen with human therapeutic doses
f. The study was designed to test safinamide only for stimulant effects.

Notwithstanding these design issues, the highest dose of safinamide (1.5 mg/kg/) evoked a response in two of the four monkeys (i.e., 50% of subjects tested), supporting positive reinforcing properties of safinamide. Therefore, a Human Abuse Potential Study (HAPS) is needed. For a description of this study see the FDA Draft Guidance for Industry, Assessment of Abuse Potential of Drugs, page 13; found at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf. We recommend that you submit the study protocol for that study for FDA review.

3. Healthy subjects administered safinamide reported somnolence, decreased attention, dizziness, and fatigue, a possible abuse potential signal. Your clinical dependence and withdrawal assessment is insufficient because a systematic evaluation of dependence, withdrawal and rebound was not performed. You will need to submit the results of an evaluation of dependence and withdrawal. For that evaluation, the duration of the observation period should be at least 3 weeks from drug discontinuation. The assessments should include reports of adverse events and of disease-specific scales using the following measures:

- Unified Parkinson’s Disease Rating Scale
- Dopamine Dysregulation Syndrome-Patient and Caregiver Inventory (DDSPC, Cabrini et al., 2009)1
- Depression Scale
- Sleepiness Scale
- Stimulant withdrawal scale (Amphetamine Withdrawal Questionnaire, AWQ)
- Physicians Withdrawal Checklist (PWC).

We recommend that you submit your proposal for the clinical evaluation of dependence and withdrawal for FDA review prior to conducting the study.

**PREScribing INFORMATION**

4. Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website, which includes:
The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
• Regulations and related guidance documents
• A sample tool illustrating the format for Highlights and Contents, and
• The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
• FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

Submit draft labeling that addresses our proposed revisions in the attached labeling.

The version of the Prescribing Information appended to this letter should be used as the base document in your Resubmission. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version in Module 1 of your resubmission. The marked-up copy should include annotations that support any proposed changes. The resubmitted labeling should include your proposed language for Section 9 (Drug Abuse and Dependence). Also, include a proposal for scheduling.

CARTON AND CONTAINER LABELING

5. Please submit draft carton and container labeling revised as follows:

We are concerned that the prominence and disparate font styles of the established name and proprietary name in the presentations on the carton and container labeling do not meet the regulatory requirements. Therefore, you should revise the established name on the proposed carton and container labeling to be in accordance with 21CFR 201.10(g)(2) which states that, “[t]he established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.”

PROPRIETARY NAME

6. Please refer to correspondence dated, February 24, 2015, which addresses the proposed proprietary name, Xadago. 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.

**PDUFA V APPLICANT INTERVIEW**

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V (‘the Program’). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Stacy Metz, PharmD, Senior Regulatory Project Manager, at (301) 796-2139.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
ODE I Acting Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**ENCLOSURE(S):**
Labeling

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT TEMPLE
03/28/2016