APPLICATION NUMBER:

207145Orig1s000

SUMMARY REVIEW
# Division Director Summary Review for Regulatory Action

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<th>Date</th>
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<tr>
<td>From</td>
<td>Eric Bastings, MD. Deputy Director.</td>
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<tr>
<td>Subject</td>
<td>Division Director Summary Review</td>
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<td>NDA/BLA #</td>
<td>207145</td>
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<td>Supplement #</td>
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<td>Applicant</td>
<td>Newron</td>
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<tr>
<td>Date of Submission</td>
<td>September 21, 2016</td>
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<td>PDUFA Goal Date</td>
<td>March 21, 2017</td>
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<tr>
<td>Proprietary Name / Non-Proprietary Name</td>
<td>Safinamide (Xadago)</td>
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<tr>
<td>Dosage Form(s) / Strength(s)</td>
<td>50 mg and 100 mg oral tablets</td>
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<td>Applicant Proposed Indication(s)/Population(s)</td>
<td>Adjunctive treatment to levodopa/carbidopa in patients with Parkinson’s disease experiencing “off” episodes</td>
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<tr>
<td>Action/Recommended Action for NME:</td>
<td>Approval</td>
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<tr>
<td>Recommended Indication/Population(s)</td>
<td>Adjunctive treatment to levodopa/carbidopa in patients with Parkinson’s disease experiencing “off” episodes</td>
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1. Introduction and Background

The submission under review is a response to a March 28, 2016, Complete Response letter that was issued for a New Drug Application for safinamide, a selective monoamine oxidase type B (MAO-B) inhibitor, initially proposed as add-on therapy to a single dopamine agonist at a stable dose in early stage Parkinson’s disease (PD) patients, and as add-on therapy to L-dopa alone or in combination with other PD drugs in mid- to late-stage Parkinson’s disease patients.

I discussed in my March 23, 2016, summary review that the safety and efficacy data submitted by the applicant should support approval of safinamide as adjunctive treatment to levodopa/carbidopa in patients with Parkinson’s disease experiencing “off” episodes, and I refer to that memorandum for a detailed discussion of the application.

A Complete Response Letter was issued in March 2016 because of deficiencies in the assessment of the abuse potential of safinamide. Specifically, the nonclinical drug discrimination study and the nonclinical self-administration study were found to be inadequate. In addition, nonclinical data in the monkey suggested positive reinforcing properties of safinamide. The evaluation of clinical dependence and withdrawal of safinamide were also determined to be insufficient, and further evaluation was requested.

This new submission primarily contains new information on the abuse potential of safinamide. It also includes a safety update.

The review team for this submission is the same as that described in my March 2016 summary review.

Of note, the indication proposed in the label included in this submission is only as adjunctive treatment to levodopa/carbidopa in patients with Parkinson’s disease (PD) experiencing “off” episodes.

2. CMC/Device

I refer the reader to my March 23, 2016, summary review for a discussion of the CMC information for safinamide. The applicant included in this new submission updated stability data that support expiration of the product after 36 months. There are no outstanding CMC deficiencies.

3. Nonclinical Pharmacology/Toxicology

I refer the reader to my March 23, 2016, summary review for a discussion of the nonclinical pharmacology/toxicology information for safinamide. The present submission does not include
new nonclinical pharmacology/toxicology information. There are no outstanding pharmacology/toxicology issues that preclude approval.

4. Clinical Pharmacology/Biopharmaceutics

I refer the reader to my March 23, 2016, summary review for a discussion of the clinical pharmacology information for safinamide. The present submission does not include new clinical pharmacology information. There are no outstanding clinical pharmacology issues that preclude approval.

As discussed in my March 23, 2016, review, the applicant did not adequately evaluate the possibility of a drug-drug interaction between safinamide and BCRP substrates, and should be asked to conduct a postmarketing study to evaluate this issue.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

I reviewed the efficacy information supporting the use of safinamide for the treatment of Parkinson’s disease in my March 23, 2016, summary review, to which I refer the reader.

Briefly, the applicant was seeking an indication as an add-on therapy in mid- to late-stage PD patients receiving L-dopa alone, or in combination with other PD medications in early stage, PD patients receiving dopamine agonist monotherapy. My conclusion in the previous review cycle was that efficacy of safinamide 50 mg to 100 mg has been established as adjunctive treatment for PD patients on stable doses of levodopa/carbidopa who experience “off time”. I also concluded that there was insufficient evidence to support a specific description in labeling of the use of safinamide.

No new efficacy information was presented in this submission, and my conclusions about the efficacy of safinamide have not changed.

7. Safety

As noted in March 23, 2016, summary review, to which I refer the reader, the safety experience for safinamide was largely as expected for a monoamine oxidase type B (MAO-B) inhibitor, with dyskinesia as most common adverse reaction in the more advanced PD population.
This submission includes a safety update, which describes data from a completed EU study in healthy subjects, synopses of results for two healthy volunteer studies completed in Japan, synopses and available safety data from ongoing Japanese Phase 3 studies, and postmarketing safety data from European countries. Based on sales data, the applicant estimates that over 10,000 patients have received treatment with at least one dose of safinamide, with over 10,000 patient-years of exposure. As discussed by Dr. Kapcala and Dr. Podskalny, there was a reported case of angioedema likely attributable to safinamide. I agree with the team’s recommendation for a contraindication in patients with a history of a hypersensitivity to safinamide.

Finally, as discussed in my March 23, 2016, summary review, I am not convinced that there is a true signal for hypotension in the safety database of safinamide, and I do not recommend a description of a risk for hypotension.

8. Advisory Committee Meeting

An advisory committee meeting was not needed for this application because two drugs of the same class are already approved, and there were no issues that needed input from an advisory committee.

9. Pediatrics

Safinamide was granted a full waiver from pediatric study requirements, because studies would be impossible or highly impracticable.

10. Other Relevant Regulatory Issues

As discussed above, deficiencies in the assessment of the abuse potential of safinamide led to the Complete Response action in the previous review cycle.

The review team has concluded that these deficiencies have been appropriately addressed, and that safinamide does not have an abuse potential. As a result, the review team does not recommend scheduling for safinamide. I agree.

In addition, Dr. Lerner, reviewer from the Controlled Substance Staff, recommends adding “a warning” in Section 2 of labeling, stating that “dosage should be reduced gradually over one week to 10 days.” As discussed by Dr. Podskalny, recommendations are already included in labeling about tapering safinamide by decreasing the dose to 50 mg for one week before stopping, so that Dr. Lerner’s recommendation is moot.
Dr. Lerner further recommends that CNS-related adverse events in clinical studies that may relate to abuse potential be described in labeling. I agree with Dr. Podskalny that a description of these events in labeling is not warranted, as the difference in incidence between safinamide and placebo for these events is very small, and not likely representative of real differences between the treatment groups.

There are no other unresolved relevant regulatory issues.

11. Labeling

There are no outstanding labeling issues.

12. Decision/Action/Risk Benefit Assessment

The applicant has adequately addressed the deficiencies in the assessment of abuse potential of safinamide that led to a Complete Response action in the previous cycle.

My conclusion about the risks and benefits of safinamide for the treatment of Parkinson’s disease have not changed since my March 23, 2016, summary review, to which I refer the reader.

Therefore, I recommend approval of safinamide as adjunctive treatment to levodopa/carbidopa in patients with Parkinson’s disease (PD) experiencing “off” episodes.

The sponsor should be required to conduct a clinical pharmacology study to evaluate the possibility of a drug-drug interaction between safinamide and BCRP substrates, as a Postmarketing Requirement.
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/s/

ERIC P BASTINGS
03/15/2017