APPLICATION NUMBER:

207145Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>NDA #</th>
<th>207145</th>
<th>NDA Supplement #</th>
<th>If NDA, Efficacy Supplement Type:</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLA #</td>
<td></td>
<td>BLA Supplement #</td>
<td><em>(an action package is not required for SE8 or SE9 supplements)</em></td>
</tr>
<tr>
<td>Proprietary Name:</td>
<td>Xadago</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Established/Proper Name:</td>
<td>Safinamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosage Form:</td>
<td>Oral Tablets</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Applicant:** Newron  
**Agent for Applicant (if applicable):** Richard Vogel  
**Division:** DNP

### NDA Application Type:
- ☒ 505(b)(1)
- ☐ 505(b)(2)

### Efficacy Supplement:
- ☐ 505(b)(1)
- ☐ 505(b)(2)

### BLA Application Type:
- ☐ 351(k)
- ☐ 351(a)

### Efficacy Supplement:
- ☐ 351(k)
- ☐ 351(a)

---

### Actions

- Proposed action  
- User Fee Goal Date is 3/29/16

### Previous actions *(specify type and date for each action taken)*

- None

### If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?

- Yes  
  - Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/ucm069965.pdf). If not submitted, explain

### Application Characteristics

- ☒ AP  
  - TA  
  - CR

---

1. The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

2. For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

3. Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Version: 2/12/16
## Review priority:
- [x] Standard
- [ ] Priority

### Chemical classification (new NDAs only):
- [ ] Type I

(Confirm chemical classification at time of approval)

- [ ] Fast Track
- [ ] Rolling Review
- [ ] Orphan drug designation
- [ ] Breakthrough Therapy designation

(Note: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

### NDAs: Subpart H
- [ ] Accelerated approval (21 CFR 314.510)
- [ ] Restricted distribution (21 CFR 314.520)

### BLAs: Subpart E
- [ ] Accelerated approval (21 CFR 601.41)
- [ ] Restricted distribution (21 CFR 601.42)

### Subpart I
- [ ] Approval based on animal studies

### REMS:
- [ ] MedGuide
- [ ] Communication Plan
- [ ] ETASU
- [ ] MedGuide w/o REMS
- [ ] REMS not required

### Submitted in response to:
- [ ] PMR
- [ ] PMC
- [ ] Pediatric Written Request

### Comments:

- Yes
- No

### BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)

- Yes
- No

### Public communications (approvals only)

- Office of Executive Programs (OEP) liaison has been notified of action
- [x] Yes
- No

- Indicate what types (if any) of information were issued
- None
- FDA Press Release
- FDA Talk Paper
- CDER Q&As
- [x] Other Snapshot

### Exclusivity

- Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?
- [x] No
- Yes

### Patent Information (NDAs only)

- Patent Information:
  - Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.
  - Verified
  - Not applicable because drug is an old antibiotic.

## CONTENTS OF ACTION PACKAGE

### Officer/Employee List

- List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)
  - [x] Included

- Documentation of consent/non-consent by officers/employees
  - [x] Included
<table>
<thead>
<tr>
<th>Action Letters</th>
<th>Action(s) and date(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>✴ Copies of all action letters <em>(including approval letter with final labeling)</em></td>
<td>RTF 7/28/14 CR 3/28/16 Approval 5/21/17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Labeling</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>✴ Package Insert <em>(write submission/communication date at upper right of first page of PI)</em></td>
<td></td>
</tr>
<tr>
<td>✴ Most recent draft labeling <em>(if it is division-proposed labeling, it should be in track-changes format)</em></td>
<td>✘ Included</td>
</tr>
<tr>
<td>✴ Original applicant-proposed labeling</td>
<td>✘ Included</td>
</tr>
<tr>
<td>✴ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <em>(write submission/communication date at upper right of first page of each piece)</em></td>
<td></td>
</tr>
<tr>
<td>✴ Most recent draft labeling <em>(if it is division-proposed labeling, it should be in track-changes format)</em></td>
<td>✘ Included</td>
</tr>
<tr>
<td>✴ Original applicant-proposed labeling</td>
<td>✘ Included</td>
</tr>
<tr>
<td>✴ Labels <em>(full color carton and immediate-container labels)</em> <em>(write submission/communication date on upper right of first page of each submission)</em></td>
<td>✘ Included</td>
</tr>
<tr>
<td>✴ Most recent draft labeling</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proprietary Name</th>
<th>Review(s) (indicate date(s))</th>
</tr>
</thead>
<tbody>
<tr>
<td>✴ Acceptability/non-acceptability letter(s) <em>(indicate date(s))</em></td>
<td>Review 10/3/14 Letter 11/9/14</td>
</tr>
<tr>
<td>✴ Review(s) <em>(indicate date(s))</em></td>
<td>Letter 11/30/16</td>
</tr>
</tbody>
</table>

| Labeling reviews *(indicate dates of reviews)*                              | RPM: ✘ None 3/6/15 DMEPA: ✘ None 8/30/15 3/21/16, 11/18/16 and 12/21/16 DMPP/PLT (DRISK): ✘ None DRISK 3/9/16 and 3/21/17 DMPP 3/22/16 and 12/22/16 OPDP: ✘ None 3/22/16 and 12/23/16 SEALD: ✘ None CSS: ✘ None Product Quality ✘ None see product quality review on carton/container Other: ✘ None |

<p>| Administrative / Regulatory Documents                                       | |
|----------------------------------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Topic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPM Filing Review/Memo of Filing Meeting (indicate date of each review)</td>
<td></td>
</tr>
<tr>
<td>All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee</td>
<td></td>
</tr>
<tr>
<td>NDAs only: Exclusivity Summary (signed by Division Director)</td>
<td></td>
</tr>
<tr>
<td>Application Integrity Policy (AIP) Status and Related Documents</td>
<td>Included</td>
</tr>
<tr>
<td></td>
<td><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></td>
</tr>
<tr>
<td>Applicant is on the AIP</td>
<td>No</td>
</tr>
<tr>
<td>This application is on the AIP</td>
<td>No</td>
</tr>
<tr>
<td>If yes, Center Director's Exception for Review memo (indicate date)</td>
<td></td>
</tr>
<tr>
<td>If yes, OC clearance for approval (indicate date of clearance communication)</td>
<td></td>
</tr>
<tr>
<td>Pediatrics (approvals only)</td>
<td></td>
</tr>
<tr>
<td>Date reviewed by PeRC 8/22/15 (Memo to File Included)</td>
<td></td>
</tr>
<tr>
<td>If PeRC review not necessary, explain: ____</td>
<td></td>
</tr>
<tr>
<td>Breakthrough Therapy Designation</td>
<td>N/A</td>
</tr>
<tr>
<td>Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</td>
<td></td>
</tr>
<tr>
<td>CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (include only the completed template(s) and not the meeting minutes)</td>
<td></td>
</tr>
<tr>
<td>CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Recession Template(s) (include only the completed template(s) and not the meeting minutes)</td>
<td></td>
</tr>
<tr>
<td>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)</td>
<td></td>
</tr>
<tr>
<td>Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)</td>
<td></td>
</tr>
<tr>
<td>Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</td>
<td></td>
</tr>
<tr>
<td>Minutes of Meetings</td>
<td></td>
</tr>
<tr>
<td>If not the first review cycle, any end-of-review meeting (indicate date of mtg)</td>
<td></td>
</tr>
<tr>
<td>Pre-NDA/BLA meeting (indicate date of mtg)</td>
<td></td>
</tr>
<tr>
<td>EOP2 meeting (indicate date of mtg)</td>
<td></td>
</tr>
<tr>
<td>Mid-cycle Communication (indicate date of mtg)</td>
<td></td>
</tr>
<tr>
<td>Late-cycle Meeting (indicate date of mtg)</td>
<td></td>
</tr>
</tbody>
</table>

4 Filing reviews for scientific disciplines are NOT required to be included in the action package.
- Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (indicate dates of mtgs)

| Advisory Committee Meeting(s) | ☑ No AC meeting |
| Date(s) of Meeting(s) |

### Decisional and Summary Memos

- Office Director Decisional Memo (indicate date for each review) None 3/28/16 and 3/21/17
- Division Director Summary Review (indicate date for each review) None 3/23/16 and 3/15/17
- Cross-Discipline Team Leader Review (indicate date for each review) None 3/22/16 and 3/19/17
- PMR/PMC Development Templates (indicate total number) None 3/6/17 (1 PMR)

### Clinical

- Clinical Team Leader Review(s) (indicate date for each review) ☑ No separate review
- Clinical review(s) (indicate date for each review) 3/27/16 and 3/19/17
- Social scientist review(s) (if OTC drug) (indicate date for each review) None
- Financial Disclosure reviews(s) or location/date if addressed in another review OR
  If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (indicate date of review/memo)
- Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) None
- Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review) ☑ N/A 12/1/15, 3/24, 16, 12/29/16, 3/9/17, and 3/17/17
- Risk Management
  - REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) n/a
  - REMS Memo(s) and letter(s) (indicate date(s)) see section 6 for DRISK review
  - Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) None
- OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators) ☑ None requested 8/18/15

### Clinical Microbiology

- Clinical Microbiology Team Leader Review(s) (indicate date for each review) None
- Clinical Microbiology Review(s) (indicate date for each review) None

### Biostatistics

- Statistical Division Director Review(s) (indicate date for each review) ☑ No separate review
- Statistical Team Leader Review(s) (indicate date for each review) ☑ No separate review
- Statistical Review(s) (indicate date for each review) ☑ None 10/23/15 final signed combined review

---

5 For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).
**Clinical Pharmacology**
- Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*
- Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*
- Clinical Pharmacology review(s) *(indicate date for each review)*
- OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*

**Nonclinical**
- Pharmacology/Toxicology Discipline Reviews
  - ADP/T Review(s) *(indicate date for each review)*
  - Supervisor Review(s) *(indicate date for each review)*
  - Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*
- Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*
- Statistical review(s) of carcinogenicity studies *(indicate date for each review)*
- ECAC/CAC report/memo of meeting
- OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*

**Product Quality**
- Product Quality Discipline Reviews
  - Tertiary review *(indicate date for each review)*
  - Secondary review (e.g., Branch Chief) *(indicate date for each review)*
  - Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*
- Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date for each review)*
- Environmental Assessment (check one) *(original and supplemental applications)*
  - Categorical Exclusion *(indicate review date/ all original applications and all efficacy supplements that could increase the patient population)*
  - Review & FONSI *(indicate date of review)*
  - Review & Environmental Impact Statement *(indicate date of each review)*

- Facilities Review/Inspection
  - Facilities inspections *(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)*

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6 Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.
<table>
<thead>
<tr>
<th>Day of Approval Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>For all 505(b)(2) applications:</td>
</tr>
<tr>
<td>- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</td>
</tr>
<tr>
<td>- Finalize 505(b)(2) assessment</td>
</tr>
<tr>
<td>For Breakthrough Therapy (BT) Designated drugs:</td>
</tr>
<tr>
<td>- Notify the CDER BT Program Manager</td>
</tr>
<tr>
<td>For products that need to be added to the flush list (generally opioids): Flush List</td>
</tr>
<tr>
<td>- Notify the Division of Online Communications, Office of Communications</td>
</tr>
<tr>
<td>Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</td>
</tr>
<tr>
<td>If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter</td>
</tr>
<tr>
<td>Ensure that proprietary name, if any, and established name are listed in the Application Product Names section of DARRTS, and that the proprietary name is identified as the “preferred” name</td>
</tr>
<tr>
<td>Ensure Pediatric Record is accurate</td>
</tr>
<tr>
<td>Send approval email within one business day to CDER-APPROVALS</td>
</tr>
</tbody>
</table>

- No changes
- New patent/exclusivity (*Notify CDER OND IO*)
- Done
- (Send email to CDER OND IO)
- Done
- Done
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STACY M METZ
03/29/2017

Reference ID: 4077212
EXCLUSIVITY SUMMARY

NDA # 207145          SUPPL #          HFD #

Trade Name  Xadago

Generic Name  Safinamide

Applicant Name  Newron Pharmaceuticals

Approval Date, If Known  3/21/17

PART I  IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?  
      YES ☒  NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no." )

      YES ☒  NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:
c) Did the applicant request exclusivity?  

YES ☒  NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

d) Has pediatric exclusivity been granted for this Active Moiety?  

YES ☐  NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?  

YES ☐  NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II    FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES  
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐  NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the
2. **Combination product.**

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#
"clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:
(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES □  NO □

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES □  NO □

Investigation #2

YES □  NO □

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support
the effectiveness of a previously approved drug product?

Investigation #1       YES ☐     NO ☐
Investigation #2       YES ☐     NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"): 

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1       !
IND #       YES ☐     ! NO ☐
              ! Explain:

Investigation #2       !
IND #       YES ☐     ! NO ☐
              ! Explain:
(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES □ NO □

Explain:

Investigation #2

YES □ NO □

Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES □ NO □

If yes, explain:

Name of person completing form: Stacy Metz, Pharm D
Title: Senior Regulatory Project Manager
Date: 3/15/17
Name of Office/Division Director signing form: Eric Bastings, MD
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STACY M METZ
03/15/2017

ERIC P BASTINGS
03/15/2017
27 January 2017

Billy Dunn, MD
Director. Division of Neurology Products
Center for Drug Evaluation and Research, FDA
CENTRAL DOCUMENT ROOM
5901-B Ammendale Road
Beltville, MD 20705

NDA 207,145
Sequence Number 079
Safinamide Oral Tablets
Indication: Parkinson’s disease
Sponsor: Newron Pharmaceuticals US, Inc.

Response to DMEPA Request:
Amendment Implementing Additional Changes to Draft Labeling

Dear Dr. Dunn:

Please refer to:
• The 26 December 2014 Resubmission of the NDA for safinamide
• The 15 December 2015 Information Request (IR) which included several DMEPA recommendations to implement changes to the draft labeling for containers, cartons, and blister packs
• The 11 January 2016 submission (SN 056) of the recommended container & carton labeling changes
• The 8 March 2016 DMEPA IR requesting additional revisions to the draft container & carton labeling
• The 21 September Resubmission of the NDA (SN 073)
• The 6 December IR for implementation of additional modifications to the container & carton labeling
• The 20 December submission implementing changes to the container and carton labeling responsive to the 6 December IR (SN 078)
• The 18 January 2017 IR concerning the container and carton labeling submitted in SN 078 and subsequent clarification in a 23 January e-mail.

The present Amendment implements the various modifications to the draft container and carton labeling requested by DMEPA in the 18 January IR. The present submission contains a Response document discussing the changes requested, a mock-ups side-by-side comparison of these changes, and the following images of the revised draft container and carton labeling:

• Professional sample carton, 50 mg, 14 tablets
• Professional sample carton, 100 mg, 14 tablets
• Bottle labeling carton, 50 mg, 30 tablets
• Bottle labeling carton, 50 mg, 90 tablets
• Bottle labeling carton, 100 mg, 30 tablets
• Bottle labeling carton, 100 mg, 90 tablets
• Bottle label, 50 mg, 30 tablets
• Bottle label, 50 mg, 90 tablets
• Bottle label, 100 mg, 30 tablets
• Bottle label, 100 mg, 90 tablets
Dr. Billy Dunn
27 January 2017

The electronic submission has been verified and confirmed to be virus free. The following software
application was used in this process: McAfee Security Center Version 5.4.0, Scan Engine

If you have any questions related to the contents of this submission, please contact me at 858-527-8093
or Dr. Stephen Graham, Executive Director of Clinical Development, Newron US (973-993-1873).

Sincerely,

Richard Vogel, PhD
Regulatory Affairs Consultant
Newron Pharmaceuticals US, Inc.
rvogel@vogelregulatory.com
NDA 207145

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Newron Pharmaceuticals US, Inc.
89 Headquarters Plaza North
Suite 306
Morristown, NJ 07960

ATTENTION: Richard Vogel, PhD
Regulatory Affairs Consultant

Dear Dr. Vogel:

Please refer to your New Drug Application (NDA) Class 2 Resubmission dated and received September 21, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Safinamid Tablets, 50 mg and 100 mg.

We also refer to your correspondence dated and received September 26, 2016, requesting review of your proposed proprietary name, Xadago.

We have completed our review of the proposed proprietary name, Xadago and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your, above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Corwin Howard, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 204.402.8654. For any other information regarding this application, contact Stacy Metz, Regulatory Project Manager in the Office of New Drugs, at 301.796.2139.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
11/30/2016
MEETING MINUTES

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xadago (safinamide) 50 mg and 100 mg Tablets.

We also refer to the meeting between representatives of your firm and the FDA on July 21, 2016. The purpose of the meeting was to ensure common understanding of the issues cited in the March 28, 2016, complete response letter and expected further steps that need to be taken before the NDA can be approved.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: End of Review

Meeting Date and Time: July 21, 2016; 1:00 – 2:00 PM EST
Meeting Location: FDA White Oak: Bldg 22/Room 1313

Application Number: NDA 207145
Product Name: Xadago (safinamide) 50 mg and 100 mg Tablets
Indication: Parkinson’s disease
Sponsor/Applicant Name: Newron Pharmaceuticals US, Inc.

Meeting Chair: Gerald Podskalny, DO, MPHS
Meeting Recorder: Stacy Metz, PharmD

FDA ATTENDEES
Gerald Podskalny, DO, MPHS, CDTL, Clinical Team Leader
Len Kapcala, MD, Clinical Reviewer
Michael Klein, PhD, CSS Director (phone)
Alicja Lerner, PhD, CSS Reviewer (phone)
Jovita Randall-Thompson, PhD, CSS Reviewer (phone)
Dominic Chiapperino, PhD, CSS Regulatory Team Leader
Luann Mckinney, PhD, Nonclinical Pharmacologist
Xiangmin Zhang, PhD, Statistical Reviewer
Aline Moukhtara, OSE, Labeling Reviewer
Stacy Metz, PharmD, Regulatory Project Manager

SPONSOR ATTENDEES
Stephen Graham, PhD, Executive Director, Clinical Development
Richard Hartman, PhD, Clinical Scientist
Richard Vogel, PhD, Regulatory Affairs Consultant
Kristen Gullo Sr., Director, Pharmaceutical Development and Regulatory Affairs, US WorldMeds
Marzia Michieletto, Regulatory Affairs Manager, Zambon SpA
1.0 BACKGROUND

The original NDA submission for safinamide for the treatment of Parkinson’s disease (PD) was submitted on May 27, 2014. The NDA was resubmitted December 26, 2014, addressing organization and navigation issues cited in the July 28, 2014, Refusal to File Letter. The review completion target was extended 3 months. The Division issued a Complete Response Letter on March 28, 2016.

The meeting request provides a briefing package for an End of Review discussion to ensure common understanding of the issues cited in the March 28, 2016, complete response letter and expected further steps that need to be taken by the Sponsor before the NDA can be approved.

FDA sent Preliminary Comments to Newron Pharmaceuticals on July 19, 2016.

2. DISCUSSION

2.1 Meeting Questions

**Question 1:** Does the FDA have any questions regarding the Sponsor’s response to the initial CSS comment concerning the data from the non-clinical drug discrimination studies?

**FDA Response to Question 1:**
No, the nonclinical abuse potential program shows the abuse potential of safinamide is low relative to Schedule II (C-II) and IV (C-IV) positive controls. Furthermore, safinamide does not have activity that is similar to substances listed under Schedule V (C-V).

In the nonclinical study assessing whether safinamide has stimulant reinforcing effects, there was limited self-administration by animals. The C-II stimulant cocaine was used as the training drug in the self-administration study. The drug discrimination findings revealed that the interoceptive properties of safinamide did not generalize to those of the C-II stimulant amphetamine.

In the study evaluating whether safinamide’s somnolence/depressant-like effects are potentially associated with an abuse response, the drug discrimination study results showed that the interoceptive properties of safinamide weakly generalized to those of the C-IV CNS depressant midazolam. These findings support the conclusion that safinamide has a low signal for abuse potential relative to drugs listed in C-IV. Without an identified positive control for the human abuse potential study (HAPS), we do not recommend that you conduct the HAPS.

In addition, safinamide lacks similar psychoactive profile of effects as drugs listed in C-V.

**Sponsor’s Pre-Meeting Comment:**
The Sponsor would like the CSS reviewer to clarify one of the comments above regarding “identified positive control,” as the last draft of the protocol for the HAP study (SN 071, 7 July) includes both amphetamine (stimulant – Schedule II) and alprazolam (depressant/sedative –
Schedule IV) as positive controls, as recommended by CSS (15 June and 24 June 2016 DNP e-mails).

**Meeting Discussion:**
Because a positive control could not be identified in the nonclinical studies (i.e., a stimulant versus a depressant/sedative), it is not possible to identify a reliable comparator for use in the HAPS. Without an identified positive control, we no longer recommend that you conduct a HAPS of safinamide.

**Question 2a:**
Does the FDA agree that the risk of abuse potential of safinamide will have been sufficiently characterized by the available clinical and nonclinical data and the results of the HAPS study?

**FDA Response to Question 2a:**
Yes. However, based on our review of the nonclinical study results, we do not recommend that you conduct the HAPS without an identified positive control.

**Sponsor’s Pre-Meeting Comment:**
See Sponsor’s comment on Question 1.

**Meeting Discussion:**
No further discussion at the meeting.

**Question 2b:**
Does the Division agree with the Sponsor’s proposed protocol for the HAP study (near final protocol is provided in the package)?

**FDA Response to Question 2b:**
See our response to 2a (above).

**Sponsor’s Pre-Meeting Comment:**
See Sponsor’s comment on Question 1.

**Meeting Discussion:**
No further discussion at the meeting.

**Question 3a:**
Results from the completed studies evaluating dependence liability in male and female rats (Reports RS1415 and RS1425, submitted in SN 059) compared with morphine, did not detect a signal suggesting dependence liability or withdrawal effects. Multiple evaluations of adverse events in PD patients during treatment (Tables 2, 3, 4 and 5), and after
discontinuation (Tables 7, 8 and 9) of long-term treatment, also did not detect any such effects.

The Sponsor will conduct the HAP study, as suggested by the CSS, and include the data in the resubmission. Based on the innocuous pattern of adverse events in PD patients while on safinamide, or after discontinuation, does the Division agree that the risk of dependence and withdrawal effects with safinamide is low, and therefore, completion of the proposed withdrawal dependence study is not mandatory for approval? The Sponsor intends to initiate this study as soon as approval of the design is received from the FDA, but would suggest that the results could be submitted as a post-approval commitment.

**FDA Response to Question 3a:**
See response to 2a (above) regarding the proposed HAPS. The dependence liability of safinamide has not been systematically evaluated. The study in rats suggests there is some withdrawal effect especially in female rats, whereas clinical data are limited but possibly indicate some withdrawal and/or rebound.

**Sponsor’s Pre-Meeting Comment:**
The Sponsor would like the Division to confirm that a dependence/withdrawal in Parkinson’s disease patients is not required (see FDA Response to Question 3b).

**Meeting Discussion:**
The sponsor was referred to the FDA’s pre-meeting response to Question 3b.

**Question 3b:**
Does the Division agree with the Sponsor’s proposed study design for a dependence, withdrawal and rebound study in patients with Parkinson’s disease (draft protocol is provided as Attachment 2 of the package)?

**FDA Response to Question 3b:**
A dependence, withdrawal and rebound study in patients with Parkinson’s disease is not required.

**Meeting Discussion:**
No further discussion at the meeting.

**Question 4:**
Does the Division agree with the Sponsor’s proposed changes to the draft Package Insert for XADAGO as presented in Attachment 4 of the package?

**FDA Response to Question 4:**
Discussions about final labeling and the carton and container labels would resume during the later stages of our review of your resubmission.
Sponsor’s Pre-Meeting Comments:
The Sponsor accepts the Division’s commitment to review the Sponsor’s proposed corrections and changes to the Package Insert.

Meeting Discussion:
The sponsor should propose edits to the Package Insert starting with the version appended to the Action Letter as the base document.

General Meeting Discussion:

Sponsor’s Pre-Meeting Comments:
The Sponsor has a few questions related to the Resubmission that are listed below.

1. The Sponsor’s understanding is that the NDA Resubmission will include the previous ISS and the additional information will be limited to the following:
   a. A Safety Update of new human data subsequent to the NDA submission, comprising:
      i. data from clinical trials in healthy subjects;
      ii. Post-marketing safety data from European countries;
      iii. Available safety data from Japanese development studies;
   b. Complete study report of the amphetamine drug discrimination study (RS1414) and final study report for the midazolam discrimination study (RS1426), performed in animals.
   c. An 8-factor analysis updated to reflect the data from the preclinical abuse liability studies.

Does the FDA agree with the Sponsor’s proposal for the updating of the safety data for the NDA Resubmission?

Meeting Discussion:
The sponsor’s proposal for the safety data for the NDA resubmission is acceptable.

2. Currently, the only additional human data that have been analyzed and reported are from four studies in healthy volunteers (2 in EU; 2 in Japan). The Sponsor is of the opinion that these data should be presented in “standalone” tables that would help expedite the Division’s review.

   Minimal safety data (all blinded) is currently available from an ongoing placebo-controlled therapeutic trial in PD patients in Japan. The Sponsor believes that these blinded data should be presented in standalone tables for notable events.

Does the FDA agree with that the new human exposure and safety data do not need to be pooled with data previously submitted in the NDA?
Meeting Discussion:

- The sponsor confirmed that there are no new safety data from open-label treatment that has not previously been submitted to the Agency during the original review cycle.

- Regarding submission of new safety information with the NDA resubmission, the sponsor will provide separate safety data for 3 groups of data: 1) healthy subjects; 2) post-marketing experience; and 3) blinded safety data (because the blind has not yet been broken) from small, ongoing Japanese development studies.

- Presentation of data from new studies in healthy subjects, post-marketing experience, and blinded Japanese trials should focus on tabulations and narrative summaries of patients with serious adverse events/deaths and discontinuations from study for treatment-emergent adverse events. For each of the 3 groups, a summary table of important features of each patient with a narrative summary should be provided as was done previously in ISS Appendix 18 (including specifying the page of the narrative summary and providing a hyperlink to the narrative summary).

3. It is the Sponsor’s understanding that, following this Class II Resubmission, the CSS recommendation will be provided to the Sponsor during / at the end of the review period.

Does the CSS agree with the Sponsor’s understanding?

Meeting Discussion:

- The Agency confirmed that an NDA submission of a Complete Response would be a Class II resubmission.

4.0 ISSUES REQUIRING FURTHER DISCUSSION
No issues require further discussion.

5.0 ACTION ITEMS
There are no action items.

6.0 ATTACHMENTS AND HANDOUTS
No attachments or handouts.
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/s/

ERIC P BASTINGS
08/18/2016
Executive CAC  
Date of Meeting: July 14, 2015

Committee: Paul Brown, Ph.D., ONDIO, Acting Chair  
Tim McGovern, Ph.D., ONDIO, Member  
Alex Jordan, Ph.D., DBRUP, Alternate Member  
David B. Hawver, Ph.D., DNP, Acting Supervisor  
LuAnn McKinney, DVM, DACVP, DNP, Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 207145  
Drug Name: Safinamide  
Sponsor: Newron Pharmaceuticals US, Inc.

Safinamide, an MAO-B selective inhibitor, is proposed for adjunctive therapy in Parkinson’s disease patients. Safinamide was negative in a battery of genotoxicity studies.

**Mouse Carcinogenicity Study**

In a 2-year carcinogenicity study, CD-1 mice (60/sex/group) were administered safinamide (in water) at oral (gavage) doses of 0, 50, 100, and 200 mg/kg/day.

Mortality in HDM was 13% greater than in control males (CM); 16 HDM survived to terminal necropsy at Study Week 105. In females, the mortality rate was similar among groups. Clinical signs consisted of convulsions, dose-exacerbated age-related findings of thin body condition, and respiratory rales in HDM and HDF. Compared to controls, body weight gain was reduced during the first 52 weeks in HDM (13%), MDF (17%), and HDF (29%), and for the remainder of the study in HDF (25%).

At terminal necropsy, there was a significant increase in fibrosarcoma in the skin in LDM; however, no significant trend was found and the finding is considered to be compatible with spontaneous neoplasia for the age and strain of mouse.

Toxicokinetic analyses were conducted during Weeks 13 and 52 to assess plasma concentrations of safinamide and two major human metabolites (NW-1153 and NW-1168); however, samples were only collected at 1 and 24 hours post dose. Therefore, exposure margins were estimated based on data from a 13-week toxicity study in CD-1 mice given 200 mg/kg/day. Plasma exposures (AUC) of safinamide at 200 mg/kg/day (the highest dose tested in the 2-year study), were ~2-fold higher than in humans taking the maximum recommended dose of 100 mg/day and similar to the AUCs for metabolites NW-1153 and NW-1689 in humans at the MRHD. A third metabolite, NW-1689 acyl-glucuronide, present in human plasma at ~7.7% of total drug-related material at the MRHD, was not detected in mouse plasma.
There were no drug-related tumors in mice administered safinamide for 2 years. The study was adequately controlled, GLP-compliant, with proper histopathology assessment and adequate exposure margins to clinical exposures at the MRHD.

**Rat Carcinogenicity Study**
In a 2-year carcinogenicity study, Sprague Dawley rats (65/sex/group) were administered safinamide (in water) at oral (gavage) doses of 0, 25, 50, and 100 mg/kg/day.

There were no statistically significant differences in mortality rate among groups in males or females. Clinical signs included convulsions, thin body, ungroomed hair coats and hair loss, hunched posture, and pulmonary rales. Body weight gain was reduced in HDM (34%) and HDF (30%), compared to controls. Retinal atrophy, a known effect of safinamide in rat, was evident clinically at Study Week 52 and increased in severity and incidence in all dosed animals through the end of the study. By Study Week 100, lenticular opacities and cataractous change obscured the retinal changes.

At terminal necropsy, there was a significant increase in thyroid C-cell carcinoma but only in LDM. In the absence of a significant trend in the incidence of C-cell carcinoma in M, the finding is considered to be anomalous.

Toxicokinetic analyses were conducted during Weeks 13 and 42 to assess plasma exposures for safinamide and two major human metabolites (NW-1153 and NW-1689). At the high dose tested in the 2-yr study, plasma exposures (AUC) for safinamide, NW-1153, and NW-1689 were ~2-fold, 5-fold, and 100-fold, respectively, those in humans at the MRHD.

There were no drug-related tumors in rats administered safinamide for 2 years. The study was adequately controlled, GLP-compliant, with proper histopathology assessment and adequate exposure margins to clinical exposures at the MRHD.

**Executive CAC Recommendations and Conclusions**

**Mouse:**

- The Committee concurred that the study was acceptable and that there were no drug-related neoplasms.

**Rat:**

- The Committee concurred that the study was acceptable and that there were no drug-related neoplasms.
Paul Brown, Ph.D.
Acting Chair, Executive CAC

cc:
/Dvision File, DNP
/LFreed, DNP
/LMcKinney, DNP
/SMetz, DNP
/ASEifried, OND IO
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/s/

ADELE S SEIFRIED
07/20/2015

PAUL C BROWN
07/20/2015
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207145

MID-CYCLE COMMUNICATION

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xadago (safinamide) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on June 9, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

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

Sincerely,

{See appended electronic signature page}

Stacy Metz, PharmD
Senior Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication
1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.
2.0 SIGNIFICANT ISSUES

Chemistry, Manufacturing and Controls (CMC)

Dissolution Method for the finished drug product
Dissolution methods are still under review.

Polymorphism and Bioavailability
Polymorphism and bioavailability considerations are still under review. The issue is whether the polymorphs might have a significant effect on bioavailability. The Division noted that there are several alternative methods to address this issue.

If there are additional follow up concerns the division will send the sponsor an IR.

Controlled Substance Staff (CSS)

Dr. Podskalny and the sponsor discussed that information described in the Abuse Liability Assessment Draft Guidance that needs to be addressed in the NDA. The sponsor will need to submit complete reports for the abuse liability studies described in the FDA’s response sent the sponsor on May 28, 2015. The sponsor agreed to submit the following:

- The requested additional analyses of the clinical trials data by the end of June 2015
- Additional Abuse Liability Studies

The sponsor will provide an estimate of when they expect to complete the abuse liability studies, and an estimate of when they anticipate submitting the final study reports to the NDA. The sponsor plans to provide these estimates by the end of June 2015. After the FDA receives the protocols, the Controlled Substance Staff will provide comment on the Abuse Liability study protocols to the sponsor.

3.0 INFORMATION REQUESTS (IRs)

Clinical Pharmacology
There is an outstanding information request concerning renal function and TEAEs and evidence regarding drug-drug interactions with proton pump inhibitors.

Controlled Substance Staff (CSS)
See CSS discussion above.
Post Mid-Cycle Communication Meeting IR Update

The sponsor provided the following information regarding the remaining requests via email on June 26, 2015.

<table>
<thead>
<tr>
<th>Information Request</th>
<th>Sponsor’s Submission Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>SN 025 6/12/15 Clinical IR re ISS file problem</td>
<td>On or before July 1, 2015</td>
</tr>
<tr>
<td>SN 027 5/28/15 CSS IR re Abuse Liability Assessment</td>
<td>On or before July 1, 2015</td>
</tr>
<tr>
<td></td>
<td>• Protocols for preclinical studies for CSS review</td>
</tr>
<tr>
<td></td>
<td>• Additional related ISS AE analyses</td>
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</table>

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns and no discussion of risk management.

5.0 ADVISORY COMMITTEE MEETING

There are no plans for an AC meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

Sponsor was informed of the following meeting date and other milestone dates:

Late Cycle Meeting: September 23, 2015
Wrap Up Meeting: October 22, 2015
Action Goal Date: December 29, 2015
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STACY M METZ
06/30/2015
Dear Review Division:

The attached template includes the necessary documentation to facilitate the required Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

**Complete the section(s) of this template that are relevant to your current submission.**

**Definitions:**

**Deferral** – A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.

**Full Waiver** – On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information MUST be included in the pediatric use section of labeling.

**Partial Waiver** – FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.
**Pediatric Assessment** – The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.

**Pediatric Plan** – A pediatric plan is the applicant’s statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.

**Pediatric Population/Patient** – 21 CFR 201.57 defines pediatric population(s) and pediatric patient(s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

**PREA Pediatric Record/Pediatric Page** – The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.
Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply:  ☑ Full Waiver  ☐ Partial Waiver  ☐ Pediatric Assessment  ☐ Deferral/Pediatric Plan

BLA/NDA#: 207145

PRODUCT PROPRIETARY NAME: Xadago Tablets  ESTABLISHED/Generic NAME: Safinamide Tablets

APPLICANT/SPONSOR: Newron Pharmaceuticals

PREVIOUSLY APPROVED INDICATION/S: None

PROPOSED INDICATION/S:

XADAGO is indicated for the treatment of patients with idiopathic Parkinson’s disease (PD) as add-on therapy to:

- A single DA-agonist at a stable dose in early-stage, patients, and
- L-dopa alone or in combination with other PD medications in mid-to-late stage patients

BLA/NDA STAMP DATE: December 29, 2014

PDUFA GOAL DATE: December 29, 2015

SUPPLEMENT TYPE: n/a

SUPPLEMENT NUMBER: n/a
Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

- [ ] active ingredient(s) (includes new combination);
- [ ] indication(s);
- [ ] dosage form;
- [ ] dosing regimen; or
- [ ] route of administration?

Did the sponsor submit an Agreed iPSP?  Yes [x] No [ ]

Did FDA confirm its agreement to the sponsor’s Agreed iPSP? Yes [x] No [ ]

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

- [ ] Yes
- [x] No

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes [x] No [ ]

If Yes, PMR # _________  NDA # _________

Does the division agree that this is a complete response to the PMR? Yes [x] No [ ]

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.
WAIVER REQUEST

**Please attach:**

- None [ ]
- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor’s proposed language, include the appropriate language under Question 4 in this form.

- Pediatric Record

1. Pediatric age group(s) to be waived.

2. Reason(s) for waiving pediatric assessment requirements (**Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division’s thinking.**)

   - Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as “Not Feasible.”) If applicable, chose from the adult-related conditions on the next page.

   - The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

   - The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

   - Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (**This reason is for Partial Waivers Only**)}
3. Provide justification for Waiver:

Studies are impossible or highly impractical because Parkinson’s Disease is an adult-related condition that does not occur in the pediatric population.

The sponsor intends to seek safinamide marketing approval only for the adjunctive treatment of adults with Parkinson’s disease.

The sponsor refers to the FDA’s Guidance for Industry: How to Comply with the Pediatric Research Equity Act (September, 2005), which lists Parkinson’s disease among the indications having “extremely limited applicability to pediatric patients because the pathophysiology of these diseases occurs for the most part in the adult population.”

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor’s proposed language:

DNP has not negotiated final language with the sponsor in this early stage of the review. The sponsor’s current language is as follows:

8.4 Pediatric Use

(b) (4)
**Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics**

These conditions qualify for waiver because studies would be impossible or highly impractical.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cancer (continued):</th>
</tr>
</thead>
<tbody>
<tr>
<td>actinic keratosis</td>
<td>follicular lymphoma</td>
</tr>
<tr>
<td>adjunctive treatment of major depressive disorder</td>
<td>gastric</td>
</tr>
<tr>
<td>age-related macular degeneration</td>
<td>hairy cell leukemia</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>hepatocellular</td>
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<tr>
<td>amyloidosis</td>
<td>indolent non-Hodgkin lymphoma</td>
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<tr>
<td>amyotrophic lateral sclerosis</td>
<td>lung (small &amp; non-small cell)</td>
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<tr>
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<td>multiple myeloma</td>
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<tr>
<td>atherosclerotic cardiovascular disease</td>
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<tr>
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<td>ovarian (non-germ cell)</td>
</tr>
<tr>
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<td>pancreatic</td>
</tr>
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<td>benign prostatic hyperplasia</td>
<td>prostate</td>
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<td>cancer:</td>
<td>refractory advanced melanoma</td>
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<tr>
<td>basal cell and squamous cell skin cancer</td>
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<td>cryoglobulinemia</td>
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<tr>
<td>endometrial</td>
<td>diabetic peripheral neuropathy / macular edema</td>
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digestive disorders (gallstones)
dry eye syndrome (keratoconjunctivitis sicca)
erectile dysfunction
essential thrombocytosis
Huntington’s chorea
infertility & reproductive technology
ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke
memory loss
menopause and perimenopausal disorders
mesothelioma
myelodysplasia
myelofibrosis & myeloproliferative disorders
osteoarthritis
overactive bladder
Parkinson’s disease
paroxysmal nocturnal hemoglobinuria
plasma cells and antibody production disorders
polycythemia vera
postmenopausal osteoporosis
prevention of stroke and systemic embolic events in atrial fibrillation
psoriatic arthritis
reduction of thrombotic cardiovascular events in patients with coronary artery disease
replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
retinal vein occlusions
stress urinary incontinence
temporary improvement in the appearance of caudal lines
treatment of incompetent great saphenous veins and varicosities
type 2 diabetic nephropathy
vascular dementia/vascular cognitive disorder/impairment
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<th>Orphan</th>
<th>Subm Status Date</th>
<th>Goal Due Date</th>
<th>Submission Classification/ Supplement Category Level Two</th>
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Reference ID: 3727113
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STACY M METZ
04/08/2015
Dear Dr. Vogel:

Please refer to your New Drug Application (NDA) dated December 26, 2014, received December 29, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Safinamide Tablets.

We also refer to your amendment(s) dated January 15, 2015, and February 10, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm). Therefore, the user fee goal date is December 29, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 29, 2015. In addition, the planned date for our internal mid-cycle review meeting is June 3, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

We have the following comments concerning your application:
Requested Controlled Substance Staff Information

Specific Recommendations for the Abuse Potential Sections of the NDA

- The Abuse Potential Section must include a scheduling proposal and basis for the proposal.
- List studies that pertain to abuse potential and dependence evaluation with functioning hyperlinks to the referenced study reports or information.
- You need to submit results from a self-administration study conducted in nonhuman primates or rodents.
- You need to submit results from nonclinical studies and clinical data on dependence, with functioning hyperlinks or you can submit the results from a devoted study of dependence.
- Clinical safety data in healthy volunteers and in patients with other disorders need to be pooled for each population, including a separate discontinuation section for each population.
- We invite you to submit protocols prior to conducting these studies, so that we may provide comment.

General Recommendations for the Abuse Potential Sections of the NDA

According to 21 CFR § 314.50 (5) (vii), the Abuse Potential section of an NDA must include a proposal for scheduling and all scientific data that form the basis of the proposal. The abuse potential assessment of a drug must include the primary data, data analyses and a discussion of the following areas:

- Chemistry (including the chemical similarity to other drugs of abuse and ability to extract the drug of abuse from the preparation).
- Pharmacokinetics and pharmacodynamics (including all data on receptor binding of the drug and its active metabolites).
- Primary data from abuse potential studies in animals including:
  - discrimination study
  - self-administration
  - dependency study
• Primary data from abuse potential studies in humans including:
  o human abuse potential study
  o dependence in humans must be assessed

• Adverse events related to abuse potential from clinical studies.

• Information and data related to abuse potential in integrated summaries of safety and efficacy (ISS and ISE).

• Information related to overdose.

• Prospective assessment of incidence of misuse, abuse, physical dependence/withdrawal syndrome, tolerance, and diversion during clinical studies.

• Epidemiological data related to abuse.

The NDA should include information and data related to abuse potential from all clinical studies, including raw data and adverse events coded with the most recent MedDRA version that includes:

• A detailed description of all adverse event reports from all clinical studies, including narratives of all incidents of abuse, misuse, overuse, or overdose (intentional or unintentional), or drug that is lost, stolen, missing, or unaccounted for, and related to drug withdrawal and withdrawal symptoms, and any other indication of dependence.

• Adverse events data related to abuse should be broken down by gender, age (non-elderly, elderly) and by population including healthy volunteers, patients with other disorders treated with safinamide, and patients with Parkinson’s disease.

• Case narratives of patients who discontinue from clinical studies for lack of compliance with study medication, study procedures, or those who discontinue participation without returning the study medication.

• Tabulation of patients who discontinued from the study, dropped out for reasons related to potential abuse and/or diversion, including narratives describing the reasons and follow-up information.

• All post-marketing safety reports of adverse events related to potential abuse.

**Requested Clinical Pharmacology Information**

1. Please submit the Bioanalytical Report for EMR701165 022 Safinamide food-effect/absolute bioavailability study.

2. The Bioanalytical Report for QT study IMPL28559 contains only information for safinamide and one metabolite (NW1153). Please submit the Bioanalytical Report for metabolites NW1689 and NW1689AG from Study IMPL28559.

3. Please submit the NONMEM control stream for base model and final model of PK and PK/PD analysis. The standards for submitting the control stream are:

   Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

**Requested Biopharmaceutics Information and Clarifications**

1. Your biowaiver request for the bridging of the film coated tablet to the earlier capsule formulation does not seem to be adequately supported by the data. Note that 21 CFR 320.22 on biowaiver requests apply to formulations that have the same dosage form. If you wish to request a biowaiver on the basis of BCS designation, please submit a supportive data package to this NDA to be forwarded to the BCS Committee for assessment. Also note that the “highly soluble” requirement for drug substances applies to the entire physiologic pH range of 1.2 to 7.5 (or 6.8), not only at a “relevant pH”.

2. Please provide the location of the report “Method development report for the in-vitro dissolution of [Redacted] 1195686-Safinamide film-coated tablets” in the NDA.

**Requested Manufacturing Process Information:**

1. It is noted in [Redacted] of the commercial batch record for the [Redacted] within Module 3.2.P.3.3 that samples are collected from the
2. Submit the following information to section 3.2.P.2.3:

3. Please revise the description of manufacturing process and controls within Module 3.2.P.3.3 to include the following information for each unit operation identified therein: batch size, equipment type, operational capacity of equipment, process parameters (target and ranges), [REDACTED] acceptance criteria).

**Requested Clinical Information**

Please submit all required financial disclosure information for study site investigators involved with pivotal trials 009, 015, and 017. Provide this information for each study in 3 sections. Section 1 should identify all investigators with no financial relationships to disclose. Section 2 should include information for all investigators with financial information to disclose. Section 3 should identify all investigators for whom you could not obtain financial information with a detailed summary of the due diligence exercised in attempting to obtain the required financial disclosures.

**Requested DMEPA Information**

1. The submitted sample label images denote “XXXXX-XXX-XX” as a placeholder in the NDC # fields. Please submit revised label images reflecting the intended product NDC #’s.

2. Please provide 3 samples of the 14-count blister packaging for both the 50 mg and 100 mg strengths.
3. Please submit tablet images depicting the imprint codes for both the 50 mg and 100 mg strengths.

**PRESCRIBING INFORMATION**

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. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- 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 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

**Contraindications in Highlights**

1. All contraindications listed in the Full Prescribing Information (FPI) must also be listed in Highlights (HL) or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

   **Comment:** The following statement is listed in the FPI, but not in the HL: **Hypersensitivity to the active substance or to any of the excipients [see DESCRIPTION (11)].**

**Adverse Reactions in Highlights**

2. For drug products other than vaccines, the verbatim **bolded** statement must be present: **“To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch”**.

   **Comment:** You need to update this information.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by March 29, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.
At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

We provided these comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. We request that you submit the requested information by March 29, 2015. If you respond to these issues later during this review cycle, we may not consider your response before we take an action on your application.

While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

**PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see [http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm](http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm). If you have any questions, call OPDP at 301-796-1200.

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.
We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

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

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Division of Neurology 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/

WILLIAM H Dunn
03/12/2015
IND 063901

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Newron Pharmaceuticals US, Inc.
89 Headquarters Plaza North, Suite 1438
Morristown, NJ 07960

ATTENTION: Richard Vogel, PhD
Regulatory Affairs Consultant

Dear Dr. Vogel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i)
of the Federal Food, Drug, and Cosmetic Act for Safinamide Tablets, 50 mg and 100mg. 

We also refer to:
- Your correspondence, dated and received August 14, 2014, requesting review of your
  proposed proprietary name, Xadago
- Your correspondence, dated and received August 25, 2014, regarding the administrative
  change

We have completed our review of the proposed proprietary name, Xadago and have concluded
that it is acceptable.

A request for proprietary name review for Xadago should be submitted once the NDA is
submitted.

If any of the proposed product characteristics as stated in your August 14, 2014, submission are
altered prior to approval of the marketing application, the proprietary name should be
resubmitted for review.

Reference ID: 3655656
If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact Tracy Peters, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2953.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Reference ID: 3655656
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
11/09/2014
NDA 207145

Newron Pharmaceuticals, S.p.A.
Attention: Richard A. Vogel, Ph.D.
Designated US Agent
5 Great Valley Parkway, Suite #350
Malvern, PA 19355

Dear Dr. Vogel:

Please refer to your May 27, 2014, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for safinamide mesylate, oral tablets, 50mg and 100mg.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the reasons described below.

NDA 207145 is materially incomplete and sections of the application lack sufficient organization to permit timely, efficient, and complete review by all relevant disciplines.

**CLINICAL**

The tables located in appendices within the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) in Module 5.3.5.3 lack sufficient organization to permit timely and efficient review. Folders labeled “iss-table-group 1 through 19” and their corresponding Table of Contents (TOC) lack pagination. A “List of Tables to Include in the ISS” located in Appendix 4 of folder “iss appendix 3-sap” lacks pagination and hyperlinks from this folder TOC to the tables in the “iss appendix” folders. The TOC of post-text tables in the ISE (Module 5.3.5.3, “Integrated Summary of Efficacy: Statistical Analysis Plan”, Appendix 3 (17.3)) also lacks pagination and hyperlinks to the corresponding post-text tables in the ISE folder. Our request for a comprehensive TOC stating the location (page numbers) with hyperlinks to each folder was included in the minutes of the pre-NDA meeting.

Tables in the ISS appendix folders marked “MAA Tables” are identified only as “Early PD” or “Late PD” and titles describing each table are not provided in the folder, therefore, each table must be opened individually, to read the title and identify a specific table. The “MAA” folders and TOC also lack pagination. Your submission does not include a comprehensive TOC that lists the page numbers with hyperlinks to the tables contained in all of the “MAA” folders. The appendix folder names do not adequately describe the contents of the folders, for example, upon examination, “iss table grp 1” appears to contain a mixture of demographic and safety...
related post-text tables from study 009. There is no apparent way to identify, refer to, or otherwise locate this information for various review needs.

The location of tables within folders “iss-table-grp-2” and “iss-table-grp-9” is different from the location tables provided in the TOC (without hyperlinks or pagination) listed in “ISS Appendix 3: SAP” TOC for these two folders.

The “Physical Examination Tables x 17.1 Groups 1-17” do not include page numbers in the TOC and the folders lack pagination.

We estimate that the appendices containing post-text tables with the deficiencies described above total more than 50,000 pages, making it impossible to navigate the ISS and ISE in a timely and efficient manner and precluding an efficient and reasonable review.

You must reorganize the appendices for the ISS and ISE.

1. Name the appendices logically to describe their contents without having to refer to a separate key.
2. Create a comprehensive TOC that provides titles for all tables in the “MAA” folders. Provide page numbers for each table with hyperlinks from the listings in the comprehensive TOC and the TOC within each folder to the listed tables.
3. Create a comprehensive TOC for all tables listed in “iss table grp” folders 1 through 19, with page numbers giving the location of each table. The TOC in each “iss table grp” folder should include hyperlinks to each table and should identify a specific page number for each table.
4. Paginate the “Integrated Summary of Efficacy: Tables” folder and provide hyperlinks to individual ISE tables and list the ISE tables in the comprehensive TOC.
5. Correct the order of the tables in folders “iss-table-grp-2” and “iss-table-grp-9” so that the order of the tables in these folders correspond to the same order listed in the ISS SAP TOC (or other comprehensive TOC) for the tables in these folders. If similar discrepancies exist between the ISS and the corresponding TOC for other post-text tables in the submission, correct those discrepancies so that the order of tables listed in the comprehensive TOC matches the TOC within the individual folders.
6. Add page numbers to the TOC and for each folder in the “Physical Examination Tables x 17.1 Groups 1-17” and paginate each folder.

We strongly recommend that you request a meeting with the FDA’s review team to assist with resolving the organization and navigation problems in the submission prior to resubmitting your application. We will honor a request for such a meeting and will make the members of the review team available for a working discussion of the actual application. During that meeting, we will ensure that you understand the issues we have described in this letter and will assist you in identifying acceptable solutions. You may also request a Reviewer Orientation Meeting (optional) to take place 45 days after resubmission of your application.
ADDITIONAL COMMENTS AND REQUESTS

We have the following additional comments and requests regarding your application that are not refuse to file issues. However, these comments should be addressed in your resubmission.

CLINICAL PHARMACOLOGY

The following Clinical Pharmacology information is needed for our review. If you have submitted this information, please provide the location of the following information in your NDA.

3. Pharmacokinetic (PK) Results sections for the following 3 trials: NW-1015-016-III-2006, MOTION, and SETTLE (similar to Section 11.4 Pharmacokinetic Results in trial NW-1015-015-III-2003).
4. Your analysis of the effect that safinamide has on ropinirole concentrations from trial 27918 (MOTION). The stated location of the analysis entitled “Newron’s analysis of the effect of safinamide treatment on ropinirole concentrations” is given as Appendix 16.5.1 (Table 2, Clinical Pharmacology Module, page 21); however, Appendix 16.5.1 contains only a report of Quintiles Analytical Study No Q-29056.

In addition, we recommend that you exclude the PK data from Study 015 in your population PK analysis. If you plan to use a population analysis to support labeling language, we suggest that you include the PK data from other studies (i.e., MOTION and SETTLE) in your population pharmacokinetic/pharmacodynamic analysis.

BIOPHARMACEUTICS

1. Provide an electronic copy of the referenced Report “Method development report for the in-vitro dissolution of 1195686-Safinamide film-coated tablets.” If you have provided this study report, please provide its location in your submission.
2. Submit the official Biowaiver request for the 50 mg RC tablet. If provided, indicate where in the application it is located.

CMC

1. The regulatory acceptance specification for safinamide should include adequate tests and analytical procedures to allow verification of each parameter reported on the manufacturer's certificate of analysis, regardless of whether the test is performed routinely on lot receipt, or periodically for vendor requalification. Therefore, revise the acceptance specification to include a quantitative test for the methanesulfonate counter ion.
2. The analytical procedures for drug substance and drug product testing are identified as translations from the test instructions. For foreign language documents, you are required to provide both the original version and an English translation. Therefore, submit copies of the original versions.

Reference ID: 3600173
3. Per 21 CFR §314.50(d)(1)(ii)(c) the application should contain the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product or a comparably detailed description of the production process for a representative batch of the drug product. Module 3.2.P.3.3 of your submission contains a very brief description of the manufacturing process. Provide the proposed commercial master batch records or comparably detailed descriptions for the commercial processes.

CARCINOGENICITY STUDY DATASETS
According to the draft guidance for carcinogenicity study design and data analysis, the submitted data have the following deficiencies,

1. You coded the animal number as “ANIMALNU”; it should be coded as “ANIMLNUM”.
2. The variables “ORGANCOD” and “TUMORCOD” contain numerical values, but they should contain character variables.

FINANCIAL DISCLOSURE
According to 21 CFR § 54.2(g), an applicant, not the applicant’s agent, is responsible for submitting the required certification (FDA Form 3454) and disclosure statements (FDA Form 3455), reporting financial interest of clinical investigators. The forms submitted with your application were signed by your US Agent. A resubmission will need to include the correct forms and proper applicant’s signature. For additional information, please see the following Guidance for Industry:

PRESCRIBING INFORMATION
In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. Prior to resubmission of your application, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website including:

- 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 42 important format items from labeling regulations and guidances.

In addition, prior to resubmission of your application and proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

PROPOSED PROPRIETARY NAME
If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions
regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@ceder.fda.gov.

**PROCEDURAL**

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA’s protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, call Tracy Peters, Senior Regulatory Project Manager, at (301) 796-2953.

Sincerely yours,

{See appended electronic signature page}

Billy Dunn, M.D.
Acting Director
Division of Neurology 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/

WILLIAM H Dunn
07/28/2014
Filing/Planning Meeting Agenda
July 10, 2014
3:00pm-4:00pm

INTRODUCTION OF APPLICATION

Application: N207145 (NME)
Drug: safinimide tablets
Sponsor: Newron Pharmaceuticals
Indication: Parkinson’s disease

SUMMARY OF IMPORTANT DATES

Stamp Date: May 29, 2014
Filing Date/Communication: July 28, 2014
Day 74 (letter if filed): August 11, 2014

Review Completion Goal Date according to GRMP:
  Primary Reviews: January 29, 2015
  Secondary Reviews: February 5, 2015
  Signatory Authority is Dr. Temple

PDUFA Goal Date: May 29, 2015

Meetings:
Additional meetings will be scheduled once a filing determination has been made

TEAM INTRODUCTIONS AND FILING REVIEW BY DISCIPLINE

Discuss potential RTF Issues; studies/info submitted; identification of info requests; day 74 letter items

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LETTER DELIVERABLES

- Time-frame for comments to RPM
- Response time if including information requests

For all applications that are being reviewed under the PDUFA V Program, the following questions need to be addressed at the filing meeting:

- Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted 30 days after receipt of the original application?
- If so, were the late submission components all submitted within 30 days?
- What late submission components, if any, arrived after 30 days?
- Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?
SAFINAMIDE FILING/PLANNING MEETING
NDA 207145
Newron Pharmaceuticals

1. Team Introductions

2. Introduction of application, including important dates:

Summary Description of Product:
Safinamide mesylate is an alpha-aminoamide, with a proposed mechanism of action that includes the selective, reversible inhibition of Monoamine Oxidase B (MAO-B) enzyme.

Newron Pharmaceuticals --Safinamide Resubmission (Parkinson’s disease)--RTF Letter sent 7/28/14

Stamp Date: 12/29/14
Filing Date: 2/27/15
Day 74 Letter Date: 3/13/15
Review Completion Goal Date according to GRMP:

Primary reviews due: September 3, 2015
Secondary reviews due: September 10, 2015

PDUFA Goal Date: 12/29/15

Upcoming Meetings:
March 11, 2015 (if needed only) and March 30, 2015
April 22, 2015
June 3, 2015 (Mid-Cycle)
June 9, 2015 (Mid-Cycle Communication)—CDTL and RPM (DD Optional)

Remaining Meetings TBD

For all applications that are being reviewed under the PDUFA V Program, the following questions need to be addressed at the filing meeting:

- Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted 30 days after receipt of the original application? No
- If so, were the late submission components all submitted within 30 days? N/A
- What late submission components, if any, arrived after 30 days? N/A
- Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? N/A
IND 63901

Newron Pharmaceuticals, S.p.A.
Attention: [Redacted], US Agent
5 Great Valley Parkway, Suite #350
Malvern, PA 19355

Dear [Redacted]:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Safinamide Tablets.

We also refer to the meeting between representatives of your firm and the FDA on September 16, 2013. The purpose of the meeting was to discuss safinamide for the treatment of Parkinson’s disease (PD).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: PreNDA
Meeting Date and Time: September 16, 2013, 10:00 - 11:00 am EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903
Application Number: IND 63901
Product Name: Safinamide Tablets
Indication: Parkinson’s disease
Sponsor Name: Newron Pharmaceuticals, S.p.A.
Meeting Chair: Eric Bastings, MD
Meeting Recorder: Stacy Metz, PharmD

FDA ATTENDEES
Eric Bastings, MD, Acting Director
William Dunn, MD, Acting Deputy Director
Gerald Podskalny, DO, MPHS Clinical Team Lead
Len Kapcala, MD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Luann Mckinney, PhD, Nonclinical Reviewer
Martha Heimann, PhD, CMC Team Lead
Angela Men, PhD, Clinical Pharmacology Team Lead
Bei Yu, PhD, Clinical Pharmacology Reviewer
Kun Jin, PhD, Statistical Team Lead
Ohid Siddiqui, PhD, Statistical Reviewer
Colleen Locicero, Associate Director of Regulatory Affairs, ODE I
Kimberly Taylor, FDA, Operations Research Analyst
Stacy Metz, PharmD, Regulatory Project Manager

EASTERN RESEARCH GROUP ATTENDEES
Patrick Zhou, Independent Assessor

SPONSOR ATTENDEES
Clinical Consultant
Richard Hartman, PhD, Clinical Scientist
1.0 BACKGROUND

IND 63,901 is indicated for Parkinson’s disease. The sponsor submitted a Type B meeting request on April 8, 2013. The purpose of the meeting is to discuss safinamide for the treatment of Parkinson’s disease (PD). Safinamide is being developed for use in early and mid-late stage PD as add-on to L-dopa and DA-agonist drugs. Background packages were received on July 1, 2013.

The meeting with DNP was delayed by the Division so the sponsor could request a Type B CMC meeting to address their CMC questions. The CMC meeting was held on August 29, 2013.

2. DISCUSSION

2.1. Chemistry, Manufacturing and Controls Questions
Questions 1-17 (all but Q6) discussed at August 29, 2013, ONDQA Meeting

Question 6:
Does the FDA agree with Newron’s strategy to control potential genotoxic impurities?

FDA Response:
Based on the information provided, it appears that your strategy for controlling potential genotoxic impurities will be acceptable. However, a final determination as to its adequacy will be a matter of review.

Sponsor’s Pre-Meeting Comment:
The Sponsor accepts the Division’s response.

Meeting Discussion:
No further discussion.

2.2. Non Clinical Development

Question 18: Adequacy of Preclinical Safety Data for Registration
Does the FDA agree that the issues have been adequately addressed and that preclinical safety data are sufficient for the registration of safinamide?
FDA Response:
On face, your nonclinical program appears sufficient to support an NDA; the adequacy of the data will be a matter of review. Regarding the retinal toxicities observed in mouse and rat, it is unlikely that the findings would be considered not relevant to humans, based solely on the nonclinical data.

Sponsor’s Pre-Meeting Comment:
The Sponsor would like to discuss the specific text above “it is unlikely that the findings would be considered not relevant to humans, based solely on the nonclinical data”. The Sponsor agrees that the retinal findings in rodents should be mentioned in the nonclinical section of the label. However, the Sponsor believes that these findings are not relevant to humans for the reasons stated below.

There is no evidence of retinal degeneration and other ocular changes noted in non-human primate studies: 39-week mono therapy and 13-week combination studies with L-dopa and pramipexole. A comprehensive ophthalmological battery of tests was performed in ~2000 patients in therapeutic studies. The tests included: visual acuity, color vision, visual fields, intra-ocular pressure, lenticular evaluations, and fundus examination, including photo micrographs of the retina. All results were reviewed by an independent rater blinded to the treatment condition. Ocular coherence tomography (OCT) was assessed longitudinally in over 300 patients on safinamide, and electro-retinograms (ERG) were performed in a single center in a limited number of patients. Review of the data, and detailed statistical analyses did not detect any systematic difference in the incidence of newly abnormal, or worsening ocular function in safinamide treated patients compared to placebo.

The Sponsor has identified sub-groups of patients who would be at high risk of retinal degeneration and these patients would be excluded from treatment with safinamide (contra-indicated in labeling). In addition, the rodent findings would be described within the Nonclinical Toxicology section of the label.

Meeting Discussion:
The Division stated that a final decision as to the clinical relevance of the retinal toxicity observed in rodents will be made based on review of all available nonclinical and clinical data. If the clinical data are considered adequate and document a lack of retinal toxicity, then concerns will be mitigated.

Additional Nonclinical Comments:

- You should ensure that each pivotal toxicology study report contains a separate signed and dated Pathology Report.

Sponsor’s Pre-Meeting Comment: The Sponsor will provide separate signed and dated Pathology reports. Historically, these reports were provided to the toxicology CROs and not within the FSR.
Meeting Discussion:
No further discussion.

- We acknowledge that you have submitted final study reports for carcinogenicity studies in mouse and rat (September 6, 2013); however, we were unable to locate the electronic datasets for either study. You should either specify the location of these datasets in the IND (serial number and date of submission) or submit them in the NDA. Without electronic datasets, we would be unable to conduct a complete independent evaluation of the study results.

Sponsor’s Pre-Meeting Comment: The Sponsor will update the IND with these datasets.

Meeting Discussion:
No further discussion.

- We were unable to locate full citations for some of the published literature referenced in your briefing package. In the NDA, you should provide full citations for all literature referenced, as well readable copies of those publications considered important for evaluation of the nonclinical data.

Sponsor’s Pre-Meeting Comment: The Sponsor will provide the full citations, as well as readable copies of critical publications, in the NDA.

Meeting Discussion:
No further discussion.

Question 19: Toxicological Characterization of Human Metabolites
Does the FDA concur with the Sponsor’s opinion that the three main human metabolites (i.e. NW-1153, NW-1689 and NW-1689 acyl glucuronide) have been adequately characterized from a toxicological point of view?

FDA Response:
Based on the information provided in the briefing package, it appears that the major circulating metabolite in humans (NW-1689) has been qualified in the nonclinical studies in rat, and that the available data for NW-1689 acyl glucuronide are sufficient to allow for an adequate evaluation. NW-1153 is a minor metabolite in human plasma and, therefore, does not need to be qualified.

Sponsor’s Pre-Meeting Comment: The Sponsor agrees with the assessment.
**Meeting Discussion:**
No further discussion.

**Question 20: Qualification of Impurities**
Does the FDA agree that the available toxicology data adequately qualify the actual impurities?

**FDA Response:**
Based on the information provided in the briefing package, the impurity appears qualified based on plasma exposure in at least one of the animal species. However, a 4-week toxicity study would not be of sufficient duration to qualify the impurity. For a drug intended for chronic administration, a 3-month toxicity in a single species would be needed, in addition to the completed in vitro genotoxicity studies.

**Sponsor’s Pre-Meeting Comment:**
The decision to undertake 2-and 4-week rat toxicity studies were based on the ICHQ3A guideline. The 4-week study included a control group.

The Sponsor believes that the has been adequately qualified by the 4-week rat study for the following reason:
- The actual content of the commercial-scale recent batches was < %, therefore the potential maximum amount of ingested by a patient mg/kg/day) is negligible and could not have a pharmacological effect. Higher content levels (as per specification) are unlikely to affect this situation. The has not been detected in man.
- There is no evidence of any in vivo in man, despite having a sensitive assay.
- No fundamental difference in toxicity was detected in the 4-week study between . Toxicology studies for the have indicated that almost all of the toxicities emerged early during treatment (i.e. within the first 2 weeks). The conduct of a 12-week study of the is unlikely to yield any new findings.

**Meeting Discussion:**
The sponsor intends to provide the levels in the drug batches used in the 4-week toxicity studies and in the 2-year carcinogenicity bioassays. Alternatively, the sponsor will consider lowering the specification limit, based on the recent data from the commercial-scale batches.

The sponsor agreed to provide a summary table of all code numbers and names used in the nonclinical study reports for the parent compound and all metabolites.
2.3 Clinical Pharmacology and Pharmacokinetics

**Question 21: Drug-Drug Interactions**
Does the FDA agree that the drug-drug interaction package performed to date is adequate to support market authorization of safinamide?

**FDA Response:**
On face, the DDI package is acceptable for a NDA submission. However, the adequacy of each study related to the DDI to support the labeling will be a review issue.

**Sponsor’s Pre-Meeting Comment:**
The Sponsor accepts the Division's position.

**Meeting Discussion:**
No further discussion.

**Question 22: Population PK/PD Analyses of Potential Drug Interactions**
Does the FDA agree to investigate potential pharmacodynamic drug interactions between safinamide and co-medications in PD patients by comparison of adverse events between safinamide- and placebo-treated patients receiving and not receiving concomitant medications?

**FDA Response:**
You should investigate potential pharmacodynamic drug interactions between safinamide and concomitant medications primarily by analyzing adverse events information. However, you should also examine other safety parameters such as vital signs, clinical laboratory analytes, and ECGs for signs of potential pharmacodynamic interaction between safinamide and other drugs.

**Sponsor’s Pre-Meeting Comment:**
The Sponsor will include these measures in the assessment of PD interactions.

You need also clarify whether the potential drug interactions between safinamide and commonly used concomitant medications in Parkinson’s disease patients will be determined using PPK/PD approach. If so, the method seems reasonable.

**Sponsor’s Pre-Meeting Comment:**
It was difficult to perform PK analyses due to the complexity of collecting plasma samples in PD patients on multiple PD medications (including immediate and sustained-release formulations), and combination treatments involving more than one medication, as well as on average 3 non-PD medications. However, the Sponsor has performed dedicated clinical interaction studies which established that safinamide does not affect the PK of drugs dependent on CYP3A4 and CYP1A2 metabolism. In addition, dedicated interaction studies in patients on L-dopa did not detect any effect of safinamide on the PK of L-dopa. Population PK
data indicated that safinamide did not have any clinically significant effect on the PK of ropinirole.

Meeting Discussion:
The sponsor will not assess potential drug interactions between safinamide and commonly used concomitant medications in PD patients using a PPK/PD approach for the reasons listed above under “sponsor’s pre-meeting comments”. The Agency acknowledged the clarification.

The following are the general expectations for submitting pharmacometric data and models:

- All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

  **Sponsor’s Pre-Meeting Comment:**
  The Sponsor will provide the above information for the reports requested.

- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

  **Sponsor’s Pre-Meeting Comment:**
  The Sponsor will provide the above information for the population PK/PD report.

- A model development decision tree and/or table that give an overview of modeling steps should be provided.

  **Sponsor’s Pre-Meeting Comment:**
  The Sponsor will provide the above information for the population PK/PD report.

- For the population analysis reports, we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

  **Sponsor’s Pre-Meeting Comment:**
  The Sponsor will provide the population PK/PD analyses for the 015 and the 016 studies, including assessment of effect of age, gender, weight, renal clearance and...
exposure to L-dopa (study 016 only). Population PK analyses were not performed for the other studies.

- In terms of where to submit the codes and data, the following folders can be used as one example for population PK related codes and data. The codes should be submitted under "module5/datasets/poppk/analysis/programs/" folder (such as run1.ctl.txt, run1.lst.txt, plot1.R.txt) with a define pdf file to explain the role of each file and sometimes with a pdf file as the revieweraid.pdf to explain the flow of running the code if necessary. The datasets should be submitted under "module5/datasets/poppk/analysis/datasets/" folder (such as poppk.xpt, pkpd.xpt) with a define pdf file to explain the variables within each data file.

**Sponsor’s Pre-Meeting Comment:**
The Sponsor agrees to provide these datasets.

**Meeting Discussion:**
No further discussion.

**Question 23: Hepatic and Renal Impairment**
Based on the findings indicated above does the FDA agree with the dosing strategy outlined above for patients with hepatic and renal impairment?

**FDA Response:**
Safinamide is an extensively metabolized drug. We recommend that you conduct a study to evaluate the PK of safinamide and its metabolites in patients with severe hepatic impairment to inform the need for dose adjustment in that patient population. Without such information, we cannot agree to a dose adjustment to 50 mg/day for patients with severe hepatic impairment.

On face, the dosing strategy for patients with mild or moderate hepatic impairment, and with any severity renal impairment seems acceptable. However, the final dosing strategy will be a review issue in the NDA.

**Sponsor’s Pre-Meeting Comment:**
The Sponsor wishes to discuss the Division’s request for a study in patients with severe hepatic impairment. The Sponsor considers that a study in patients with severe hepatic impairment is not required as these patients will be excluded from treatment with safinamide. The Sponsor agrees with the Division that the dose should be limited to 50mg/day for patients with moderate hepatic impairment.

The Sponsor agrees with the Division’s assessment of the dosing strategy in patients with renal impairment.
Meeting Discussion:
The Agency’s acknowledged that the sponsor believes safinamide should be contraindicated in patients with severe hepatic function; therefore, the sponsor will not conduct a PK study in patients with severe hepatic impairment.

Question 24: QTc and Tyramine
Does the FDA agree that no specific precautions are warranted, relating to QTc or tyramine restriction?

FDA Response:
This is a matter of review.

Sponsor’s Pre-Meeting Comment:
The Sponsor accepts the Division’s position.

Meeting Discussion:
No further discussion.

2.4 Safety and Efficacy

Question 25: Long-term Efficacy
Does the FDA agree that these data should be presented in labeling to inform prescribers and patients of the long-term efficacy of safinamide?

FDA Response:
The results for the primary efficacy endpoint in your long-term trial did not show that either safinamide dose was statistically superior to placebo. In study 18, the analysis plan did not permit analysis of secondary efficacy endpoints within the hierarchy once the results for the primary efficacy endpoint failed to show that safinamide was superior to placebo. The results for the list of secondary endpoints for study 18 are not statistically significant and they are not eligible for testing according to the statistical analysis plan; therefore, these results would not appear in the label.

Sponsor’s Pre-Meeting Comment:
The 016/018 trials are the first 2-year placebo-controlled studies of an investigational agent in patients in mid- to late-stage PD treated with L-dopa and other PD medications. The Sponsor believes that the findings of a treatment benefit that is preserved at 2 years for both the 50 and 100 mg doses for ON time without any dyskinesia is important for prescribers, patients and caregivers. The Sponsor suggests that these data be appropriately described in the Clinical Trials Results section of the package insert.
Meeting Discussion:
The lack of statistical significance for the primary efficacy endpoint in the extension trial diminishes the likelihood that efficacy results from this trial will appear in the label. Nevertheless, the Agency will review the results of this trial and determine whether any information from this trial might be described in the label.

The sponsor suggested that results from the extension trial should be included in the Clinical Trials section of the label. However, the Agency noted that inclusion of such information in that section is tantamount to a claim and therefore there is no guarantee that any information from this trial would be described in the label.

Question 26: Study 009 – Acceptability as a Pivotal Study
Does the FDA agree that the results of Study 009 can be used to demonstrate the efficacy of safinamide although derived from a study of 3 months duration, as this study was performed in accordance with the existing guidelines? (EMA/EWP/563/95 Rev.1, which preceded the current guidelines EMA/CHMP/330418/2012 Rev.2, released 21 June 2012.)

FDA Response:
No. We have concerns about the results of this relatively small phase 2 trial. The primary efficacy endpoint for study 009, the responder rate for patients experiencing ≥ 30 % improvement in Part III of the UPDRS, has not served as the primary endpoint in pivotal studies for drugs approved for the treatment of early Parkinson’s disease. The change from baseline in UPDRS Part III, Parts II + III, or Parts I+II+III have traditionally served as the primary efficacy endpoint in trials for new drugs used to treat early Parkinson’s disease. The results of the blinded data analysis for the change from baseline for Part III and Part II of the UPDRS in the April 2003 final study report 009 (performed according to the July 2002 final Statistical Analysis Plan) were not statistically significant for either safinamide dose (0.5 mg/kg/day or 1.0 mg/kg/day) compared to placebo, which suggests the findings were not robust. The average doses of safinamide administered in this trial were approximately 38 mg and 75 mg; however, you do not intend to base the recommended dose of safinamide on patient weight.

Sponsor’s Pre-Meeting Comment:
Study 009 was the first study performed to evaluate a dopaminergic treatment as add-on to a dopamine agonist in patients with early PD, and was designed to detect a treatment difference of 33% in “responders” (defined as 30% improvement from baseline in UPDRS III) assuming a 15% placebo response rate. The sample size calculation indicated a need for approximately 50 patients per group, assuming a 20% drop-out rate. The study results, using inferential statistics, indicate that the assumptions for study size were correct and provided compelling evidence of the efficacy of safinamide on the primary efficacy measure. The study was designed based on response data in early PD patients available at that time (2000).

Experts in PD (Movement Disorders Society, 2003; Schrag, et al, 2006; Hauser, et al, 2011, Shulman, et al, 2010) have indicated that results of new trials should be based on Minimal Clinically Important Change (MCIC). For the UPDRS III in patients with early PD, the range
corresponding to the MCIC is approximately 2-3 points. On average, this corresponds to less than 30% of the mean baseline score.

We agree with the Division that the responder rates analyses do not reflect the changes in the entire population. Therefore, in Study 009 the secondary variable addressed this by analyzing the mean change in UPDRS III. The test for assumption of normality for the ANCOVA model was not appropriately assessed and led to the incorrect statistical method that was cited in the first study report. Recognizing the mistake, the pre-specified and correct statistical model was used and the CSR updated with the new result. No changes were made to the efficacy data prior to the re-analysis.

Does the FDA agree that the highly statistically significant results obtained (both for the ITT and the DA-agonist monotherapy populations) for the 1.0 mg/kg/day dose (~80 mg/day) from analyses of responder rates (clinically relevant benefit defined as ≥30% improvement from baseline in UPDRS-III) that was defined as the primary efficacy variable? Furthermore, does the FDA agreed that the finding of a significant improvement in UPDRS III mean change for the 0.5 mg/kg group (~40mg/day) qualify it as the “minimally effective dose”?

FDA Response:
Please refer to our response on the acceptability of results from Study 009.

Sponsor’s Pre-Meeting Comment:
Please refer to our response above for Question 26.

Meeting Discussion:
The Agency’s views the results from Study 9 as not adequately showing that safinamide is effective for the treatment of patients with Parkinson's disease who are not experiencing motor fluctuations, because of the concerns outlined in the Agency’s Preliminary Response. The Agency also noted that it is highly unusual to accept a post hoc revision of the analysis plan when the protocol specified primary analysis was not statistically significant. The sponsor should provide a detailed justification for using the revised analysis in the NDA.

Question 27: Study 015
In light of the good tolerability and safety associated with the 50-100 mg/day dose and the evidence of benefit both during short and long term treatment, does the FDA agree that the results for the 50-100 mg/day dose could be considered as valid?

FDA Response:
We do not find the results for the 50-100 mg dose in Study 015 show that safinamide is effective for the treatment of patients with early Parkinson’s disease. The analysis of the primary endpoint for the high dose of safinamide (target 200 mg daily) did not show that safinamide was superior to placebo (P > 0.05). Your statistical plan only permitted testing of the low dose (100 mg) safinamide group if the high dose (200 mg) safinamide group was statistically superior to placebo on the primary efficacy endpoint. The finding of an inverse dose response for patients treated with safinamide lacks biological plausibility. The accidental dosing of patients with
safinamide who were randomized to placebo treatment also raises concerns about the trial conduct.

**Sponsor’s Pre-Meeting Comment:**

1) The finding is counter-intuitive but not uncommon with PD treatments (see below) and other CNS drugs.

   - **Rasagiline:**
     TEMPO – Response in 1mg/day group was ~ 1.5 times (2.7 vs 1.7 points for UPDRS III) the benefit in the 2mg/day group.

   - **Rotigotine:**
     SP511 – U-shaped dose response curve with 9mg and 27mg better than 18mg.
     SP650 – Mean change in OFF time better for 18mg (-1.8 hrs) versus 27mg (-1.2 hrs)

   - **Tozadenant:**
     SYN115-CL02 – Inverted U-shaped dose response curve with 120mg better than lower or higher doses for “ON Time”

2) The 150-200mg dose is associated with a significantly higher drop-out rate (20%) versus the 50-100mg and placebo (10%) suggesting dose related adverse outcome.

3) The effect of the 50-100mg dose is consistent in the MMRM, LOCF, and OC+RDO analyses. Furthermore, the 50-100mg dose, but not the 150-200mg dose, also showed superiority over placebo at 18 months on the new UPDRS III mean change, responder rate, UPDRS II, and EuroQoL. The presence of a small number of safinamide capsules in the placebo supplies is the only deficiency noted in the conduct of the trial.

**Meeting Discussion:**

Although the sponsor argued that “low” dose safinamide is superior to placebo, the Agency noted that the failure to show superiority of “high” dose safinamide over placebo precluded analysis of “low” dose safinamide based upon the prespecified hierarchical Statistical Analysis Plan. The sponsor should include all relevant arguments for their position in the NDA.

**Question 28: Exclusion of Protocol Violators in MOTION**

Although this analysis was performed post hoc, does the FDA agree that the results should be considered as valid, as the reasons for exclusion of these patients are clearly evident?

**FDA Response:**

No. We do not believe post hoc revisions to the primary efficacy analysis in a subgroup identified after unblinding of the trial data are valid. Meta-analyses or analyses of pooled data from multiple efficacy trials do not constitute evidence of effectiveness when the primary analyses of these trials do not show the drug is effective. We primarily rely on analyses of individual trial results based on the pre-specified primary analyses of the primary efficacy endpoint, in the ITT or mITT population, as specified in the Statistical Analysis Plans (SAPs).
Sponsor’s Pre-Meeting Comment:
The primary comparison as planned in the ITT population (LOCF ANCOVA) is illustrated below.

<table>
<thead>
<tr>
<th>Statistic</th>
<th>50 mg/day</th>
<th>100 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS Mean difference vs. Placebo (SE)</td>
<td>-0.65 (0.58)</td>
<td>-1.04 (0.58)</td>
</tr>
<tr>
<td>[95% Confidence interval]</td>
<td>[-1.79, 0.48]</td>
<td>[-2.17, 0.10]</td>
</tr>
<tr>
<td>p-value</td>
<td>0.259</td>
<td>0.073</td>
</tr>
</tbody>
</table>

As the treatment effect in this study differed from the previous studies, the Sponsor reviewed the populations to determine the reasons. Prior to unblinding, the Sponsor classified these patients as major protocol violators (failure to satisfy the basic eligibility criteria for the indication – i.e., dopamine agonist monotherapy at a stable dose); however, these patients were not excluded from the ITT or the mITT analyses as permitted by the ICHE9 guidance (page 28):

“There are a limited number of circumstances that might lead to excluding randomized subjects from the full analysis set, including the failure to satisfy major entry criteria (eligibility violations), the failure to take at least one dose of trial medication, and the lack of any data post randomization. Such exclusions should always be justified. Subjects who fail to satisfy an entry criterion may be excluded from the analysis without the possibility of introducing bias only under the following circumstances:

a. The entry criterion was measured prior to randomization.
b. The detection of the relevant eligibility violations can be made completely objectively.
c. All subjects receive equal scrutiny for eligibility violations. (This may be difficult to ensure in an open-label study, or even in a double-blind study if the data are unblinded prior to the scrutiny, emphasizing the importance of blind review).
d. All detected violations of the particular entry criterion are excluded”

The current Sponsor performed the appropriate analyses excluding these patients to obtain the results for the dopamine agonist monotherapy population.

The results of the ITT and dopamine agonist monotherapy populations indicate that the 100mg dose versus placebo was significant for the secondary endpoints of UPDRS II (ADL) and the patient-rated outcomes of PDQ-39 and EQ-5D.

The mITT population also did not exclude the patients who violated the entry criterion of dopamine agonist monotherapy at stable doses, but excluded one patient who did not have a post-baseline assessment.
Meeting Discussion:
The Agency voiced the concern that exclusion of a relatively small number of patients had a significant effect on the treatment difference of safinamide (versus placebo) and on the corresponding p value. The Agency further noted that inclusion of protocol violators in the primary analysis of the mITT population in pivotal trials usually does not dramatically change the efficacy results for drugs with robust treatment effect.

2.5. Labeling Issues

Question 29: Target Product Profile (Draft Labeling)
The FDA’s feedback on the proposed INDICATION and other aspects of the draft labeling is requested.

FDA Response:
Discussions regarding the contents of the label are appropriate after we have started to review of your NDA. However, based upon your preliminary presentation of the clinical trials information, it is difficult to conclude that safinamide is effective for treating patients with early Parkinson's disease receiving concomitant treatment with a dopaminergic agonist.

Sponsor’s Pre-Meeting Comment:
The Sponsor would like to discuss with the Division the arguments presented above in support of the efficacy of safinamide for the dopamine agonist add-on indication.

The Sponsor would also like to discuss the Division’s review of the SETTLE (27919) study in support of the L-dopa add-on indication.

Additional Comments

- You should present the primary analysis of the primary efficacy endpoint (and other important efficacy endpoints) in the modified Intent-To-Treat (mITT) population in each treatment group. The mITT population includes all patients who had a baseline evaluation, received at least one dose of study medication and had at least one post-baseline efficacy assessment. Your presentation of the results for several trials (15, 16, 18, SETTLE, MOTION) show discrepancies with regard to the number of patients in the ITT population and the number of patients that should be in the primary analysis of the mITT. Some of the patients included in the ITT and mITT population do not appear to have data documenting a baseline and post-baseline efficacy assessment. Your NDA should present efficacy analyses for the mITT population for all pivotal trials.

Sponsor’s Pre-Meeting Comment: The Sponsor acknowledges the Division’s request and will provide analyses in both ITT and mITT populations.
Meeting Discussion:
• The sponsor’s tables indicate that some patients from several studies did not have a baseline and a post-treatment assessment of the primary efficacy endpoint; therefore, they were not eligible to be included primary analysis of the primary endpoint in the mITT population. The protocol specified analysis of the primary efficacy endpoint is limited to patients meeting criteria for inclusion for the mITT population.

• You noted that the database was locked, then unlocked and relocked several times during the analysis of Studies 16 and 18. Please provide a complete listing of the data revisions that occurred with each unlocking and relocking of the database and justify the need to reopen the database after database lock for each instance. Please submit analyses for the primary efficacy endpoint (i.e., change of “ON” time without troublesome dyskinesia) and the key secondary efficacy endpoint (i.e., change of “OFF” time) for all statistical analyses (including results and N for each treatment group, statistical approach applied, and respective p values) for Study 16 and/or Study 18 following the initial database lock and for and for all subsequent episodes of unlocking and relocking of the database in these studies.

Sponsor’s Pre-Meeting Comment:
The Sponsor acknowledges the Division’s request and will provide analyses in both ITT and mITT populations.

Meeting Discussion:
No further discussion.

• Although you did not ask any specific questions about your planned Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) in your meeting briefing package, you have submitted yours plans for your ISS and ISE, separately. We plan to provide recommendations/comments on these plans in the final meeting minutes.

Sponsor’s Pre-Meeting Comment:
The Sponsor looks forward to receiving these recommendations/comments.

Meeting Discussion:
The Agency will include recommendations for analyses in the ISS and ISE in the final meeting minutes. The sponsor should contact the Division to discuss proposed changes to the Division’s recommendations and requests regarding the content and format of the analyses in the ISS and the analyses in the ISE.

• We emphasize that the NDA must be complete when you submit the application. An incomplete application may not be filed.
**Sponsor’s Pre-Meeting Comment:**
The Sponsor understands this.

**Meeting Discussion:**
No further discussion.

- We also recommend that you follow the guidelines for electronic submission of your NDA and all datasets. You can consult with FDA colleagues who specialize in these electronic submissions if you have any questions.

**Sponsor’s Pre-Meeting Comment:**
The Sponsor understands this.

**Meeting Discussion:**
No further discussion.

**General OCP comments:**

1. Please provide the clinical pharmacology summary as review aid according to the format provided in the Appendix.
2. Please provide a thorough justification for the lack of potential DDI through CYP isoenzyme and transporter systems (see Clinical pharmacology Guidance for Industry - Drug Interaction Studies: Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations).
3. Please clarify whether the impact of age (including young and > 65yr patients) on safinamide PK has been evaluated via PPK approach.

**Sponsor’s Pre-Meeting Comment:**
All of the items will be addressed in the NDA submission.

**Additional OCP question:** Food delayed the drug absorption for < 1 hour without affecting the extension of drug absorption. Clarify why you are proposing in your dosing regimen to take the drug with breakfast?

**Sponsor’s Pre-Meeting Comment:**
In studies performed to date, patients were asked to take safinamide with breakfast as this would allow for plasma samples to be taken at Tmax (2-3hrs post-dose). This recommendation was not based on any effect of food on the absorption of safinamide.

**Meeting Discussion:**
No further discussion.
3.0 ADDITIONAL ITEMS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that no risks that require a REMS have been identified by the sponsor so they did not plan to submit a REMS.

Sponsor’s Pre-Meeting Comment:
The Sponsor has noted the FDA comments and suggestions. Based on a benefit-risk assessment of completed pre-clinical and clinical studies, the Sponsor has not detected any toxicity that requires a risk management plan beyond routine clinical observation and precautions. The Sponsor will address any risks requiring mitigation or further characterization identified in the ISS through appropriate measures.

In addition, we note that a chemistry pre-submission meeting was held on August 29, 2013. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.
For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

After January 5, 2014, FDA will strongly encourage sponsors to submit their PSP prior to the initiation of Phase 3 studies and the PSP must be submitted no later than 210 days prior to submission of application. Therefore, DNP encourages you to submit your PSP as soon as possible based on your possible planned submission by the end of March 2014. Applications submitted on or after January 5, 2014 without an agreed PSP are at risk of receiving a Refuse to File.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms 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 following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address...
where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Federal Establishment Indicator (FEI) or Registration Number (CFN)</th>
<th>Drug Master File Number (if applicable)</th>
<th>Manufacturing Step(s) or Type of Testing [Establishment function]</th>
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<td>2.</td>
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Corresponding names and titles of onsite contact:

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<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Onsite Contact (Person, Title)</th>
<th>Phone and Fax number</th>
<th>Email address</th>
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**4.0  ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion.

**5.0  ACTION ITEMS**

There were no action items.

**6.0  ATTACHMENTS AND HANDOUTS**

The sponsor provided a handout of their responses to our preliminary responses. Those responses have been incorporated in the minutes.

The following items have been included as attachments:
Appendix I
DNP Requests for ISS and ISE Analysis Plans

Appendix II
Clinical Pharmacology Appendix (referred to in #1 General OCP Comments) is attached.
APPENDIX I

MEDICAL OFFICER REQUESTS FOR ISS AND ISE ANALYSIS PLANS

ISS

General

• All patients randomized and treated should be included in the safety analyses.

• Conduct all safety analyses requested here for the following trials according to the randomized treatment including targeted safinamide dose:

  o Study 9 (placebo, 0.5 mg/kg/day, 1.0 mg/kg/day, all safinamide doses)
  o Study 15 (placebo, 100 mg, 200 mg, all safinamide doses)
  o Study 17 (placebo, 100 mg, 200 mg, all safinamide doses)
  o Study MOTION (placebo, 50 mg, 100 mg, all safinamide doses)
  o Study MOTION EXTENSION (placebo, 50 mg, 100 mg, all safinamide doses)
  o Study 16 (placebo, 50 mg, 100 mg, all safinamide doses)
  o Study 18 (placebo, 50 mg, 100 mg, all safinamide doses)
  o Study SETTLE (placebo, 100 mg)
  o Pool of Study 15 and 17 (placebo, 100 mg, 200 mg, all safinamide doses) This analysis considers both of these trials as a single trial.
  o Pool of Study MOTION and MOTION EXTENSION (placebo, 50 mg, 100 mg, all safinamide doses) This analysis considers both of these trials as a single trial.
  o Pool of Study 16 and 18 (placebo, 50 mg, 100 mg, all safinamide doses) This analysis considers both of these trials as a single trial.
  o Pool of Study 15 and MOTION (placebo, 50mg, 100 mg, 200 mg, all safinamide doses)
  o Pool of Study 16 and SETTLE (placebo, 50 mg, 100 mg, all safinamide doses)

We believe that every patient randomized to receive safinamide was randomized to receive a specific target dose and that titration to that dose was conducted according to the protocol. If there was a problem with tolerability or adverse event(s), the patient could receive a lower safinamide dose. We are especially interested in analyses according to the randomized, targeted dose. For example, if a patient was randomized to receive 100 mg but was not able tolerate 100 mg and had to receive a lower dose (e.g., 50 mg), in our desired analysis according to randomized, targeted dose, such a patient would be analyzed in the 100 mg dose group and not in the 50 mg dose group. We are also requesting analyses according to actual dose received based upon the modal dose in a trial.

Please contact the division if there are any errors in the above outline of the randomized, targeted doses for each trial.

• Conduct all safety analyses recommended here also for modal, actual dose of safinamide (and all safinamide doses) received during the whole trial.

• For the randomized, double-blinded, controlled trials (and pooled analyses), we are requesting analytical comparisons of safinamide dose to present all safety results for all analyses on the same page according to randomized treatment (i.e., placebo or safinamide randomized, targeted dose, and all doses).

Reference ID: 3391076
• Present all safety analyses recommended here also for open-label treatment by pooling results of all open-label treatment.

• Please also conduct all safety analyses (for all recommended analyses for TEAEs, clinical laboratory analytes, orthostatic vital signs, ECGs) according to various subgroups of patients:
  o regional subgroups
    ▪ North America vs outside of North America
    ▪ North America vs Western Europe vs all other regions combined (i.e., Eastern Europe, Latin America, Asia, Africa)
  o males vs females
  o patients > 65 years old vs < 65 years old
  o presence or absence of concomitant treatment with at least one dopaminergic agonist
  o presence or absence of concomitant treatment with any drug that lowers blood pressure (e.g., antihypertensive drugs and vasodilators)
  o race (when a race accounts for > 5% of patients)

• Please present cumulative dose-duration exposure tables based upon the modal actual safinamide dose received for the whole exposure and show exposure for “any” safinamide dose, for any treatment time, > 6 > 12, > 18, and > 24 months treatment. In cumulative exposure tables, patients treated for longer periods are also included in exposure results for shorter periods. You may show results for treatment periods longer than 24 months if such data are available. You can combine controlled and open-label treatment in these dose-duration exposure tables.

• Present all analyses (central tendency and outliers) for each safety parameter (e.g., vital signs, clinical laboratory analytes, ECG parameters) over time (showing baseline and results from all post baseline visits until the end of the trial). Central tendency analyses should include mean data and other descriptive parameters. Outlier analyses should show the numerator relative to denominator and respective %.

• Present results for incidence for all outlier analyses (for orthostatic VS, clinical laboratory analytes, ECG parameters) according to time perspective of “any” visit and also at “final” visit.

• Present all central tendency analyses for the mean absolute result and for the mean change from baseline for each safety parameter (i.e., orthostatic vital signs, clinical laboratory analytes, ECG parameters).

• Please interpret and discuss all analyses presented in the ISS within the ISS. Whenever there is a need to refer to any data within the ISS or “outside” of the ISS, hyperlinks to these data should be provided.

• Please include a detailed Table of Contents (TOC) for the ISS with a list of all tables, figures, and listings and ensure the ability to hyperlink to any page shown in the TOC. Please do the same for every report and document in the NDA.

• It is not necessary to conduct statistical analyses for safety data. Although it is all right for you to do so. We do not expect statistical analyses for safety data. Instead, we expect descriptive analyses. Because safety outcomes are not powered to show statistical significant, the lack of statistical significance (i.e., p < 0.05) for any safety outcome does not indicate that there is no basis for a safety concern.
• We recommend that you submit shells of the planned safety analyses (including all Agency recommended analyses) for review and feedback after reviewing the Agency recommendations. Because many of these analyses will follow the same format, it is not necessary that a shell be presented for each safety analysis when the format is identical. Prototypical shells of all these data can be submitted for review and feedback. Once you have determined the specific format for individual trial and integrated/pooled analyses, we recommend that you submit a list with descriptive names of all tables) of individual safety analyses planned (including all Agency recommended analyses), that would follow specific formats, for DNP review and feedback. Submission of this list for our review will help ensure that you are planning to submit all the safety analyses that we want and have requested.

• Please ensure that the ISS is electronically constructed accurately/correctly to show appropriate page coordination in every situation. For example, the page number shown in the table of contents should be the same page number shown on the page after one hyperlinks to that page and when a print command is given to print that page.

• We recommend that you review the following guidances for assistance in planning your NDA submission in general but in particular for planning the details about the format and content of your ISS:
  • Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review
  • Guidance for Industry M4: The CTD — Efficacy Questions and Answers
  • Format and Content of Clinical and Statistical Sections of Application
  • Format and Content of the Summary for New Drug and Antibiotic Applications
  • Formatting, Assembling and Submitting New Drug and Antibiotic Applications
  • Regulatory Submissions in Electronic Format; General Considerations

You can contact the division for advice if unusual questions arise as to the content and format of your submission and the answers are not contained in any of these guidances.

• We recommend that you provide a tabular summary of all study sites for each phase 2 and 3 trial including information about the principal investigator (i.e., address, phone, Fax, e-mail) and patients studied (i.e., # of patients screened, randomized/treated, completing the trial).

• To help facilitate a reviewer’s ability to access desired tables, please provide an overall table for each general safety category (e.g., adverse events, laboratory, vital signs, ECGs) that provides hyperlinks to key tabular analyses.

• In addition to all the safety analyses we are requesting, you are may submit any other safety analyses that you deem important.

• The Appendix outlines and describes all safety analyses that we are requesting for submission in your NDA. Please contact us if there is any question about deviating from the content and format of safety analyses we have requested.
Adverse Events

- Please provide summary tables for all treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs causing study discontinuation from a time perspective and from a dose-perspective (as previously outlined) for the controlled trial data and open-label trial data. All of these TEAE data should be presented for:

  1) the whole trial treatment period for any TEAE with onset at any time in the whole trial;

  2) titration/dose adjustment period: The titration period for each trial is defined as the protocol specified titration period to achieve the highest randomized, targeted safinamide dose in a trial plus the time interval between protocol specified titration increments. For example, if the protocol specified that a patient initiate treatment with 50 mg safinamide and increased to 100 mg after 2 weeks (14 days) treatment, the titration period would be considered to be 4 weeks (2 weeks to achieve the highest dose + the 2 week time interval for increasing dose). Consequently, the end of the titration period should always be longer than the time to reach the highest targeted dose according to the protocol-specified titration.

  3) maintenance period (the period after the titration period until the end of the trial or end of treatment for patients who discontinue prematurely) for any TEAE with onset in this period; and

  4) “persistent” TEAEs from the titration period into the maintenance period for a certain period of time (we recommend ≥ 7 days for this definition of “persistent”).

All time requests for time perspective analyses for titration period, maintenance period, and persisting event from titration period into maintenance period (for TEAEs, clinical laboratory analytes, orthostatic vital signs, ECGs) are only applicable to trials or pools of trials involving a titration period. Because Studies 17, 18, and MOTION EXTENSION did not include a titration period, time perspective analyses for titration period, maintenance period, and persistent event from titration period into maintenance period are not required/possible. These latter trials should be analyzed for safety for the whole treatment period and also for the final visit for outlier analyses for clinical laboratory analytes, orthostatic vital signs, and ECGs.

Analyses of TEAEs according to a time perspective can very helpful in characterizing the risks of certain TEAEs at particular times relative to treatment.

- Please provide a definition of TEAE including the time after the last treatment dosing for considering that an adverse experience is a TEAE. Ordinarily, we recommend that a TEAE be considered as any adverse event developing during treatment or as an adverse event present at baseline/pre-treatment that became worse during treatment. Adverse events occurring up to a certain period (e.g., 30 days) after the last day of treatment should also considered as a TEAE.

- Please present all 3 categories of narrative summaries (i.e., SAEs, discontinuations for TEAEs, TEAEs of special interest) associated with safinamide treatment in a single location in the ISS. Within each of the 3 categories, present narratives according to study. Please construct each narrative summary chronologically with the aim of making each summary as comprehensible as possible. To facilitate better construction of narrative summaries for maximal comprehension of each narrative summary, we recommend that you note:
  1) dates of onset and resolution (or days after starting investigational treatment) for onset of signs/symptoms

Reference ID: 3391076
of the TEAE and their resolution; 2) pertinent positives and negatives for the TEAE prompting the narrative; 3) starting and stopping dates of concomitant medications and doses; 4) supportive medical data (e.g., results of X rays or other imaging, laboratory tests and notation if abnormal, ECGs etc.); and 5) the chronological course of each patient including outcome.

Please also provide a comprehensive listing of all patients and adverse events prompting a narrative summary at the beginning of the section containing narratives and specify the page location of each subject’s narrative and provide a hyperlink to the narrative. Please hyperlink the term(s) describing the TEAE in the comprehensive list of all narratives to the specific section of the narrative dealing with that specific TEAE. This specific request is made because some chronological narratives can be long and complex extending over several paragraphs or pages. Hyperlink all references (within a study report) to a specific patient experiencing a TEAE requiring a narrative to the specific narrative located in the ISS section.

This listing should outline the following information:
- patient ID #
- age
- gender
- specific TEAE
- type/category of TEAE prompting a narrative summary
- outcome
- daily safinamide dose

- We recommend MedDRA coding for adverse events. Please specify the version of MedRA used and use the same version for all coding for the ISS analysis Safety datasets.

- Include the adverse event coding dictionary (filing issue) as a PDF file and show: 1) how investigator verbatim terms were mapped to preferred terms and 2) also how preferred terms are mapped to investigator verbatim terms.

- If you present any analyses according to investigator assessment of causality, we recommend that you use a binary categorization as “unlikely” (e.g., combining “unrelated” and “unlikely,” and combining “possible” and probable”).

- We are recommending “worst case” analyses that show the incidence of adverse events possibly suggestive of hypotension/orthostatic hypotension and also possibly suggestive of falls for the controlled trials according to treatment and the time and dose perspectives outlined previously. For conducting such analyses, we recommend that you determine a case definition based upon a variety of adverse event terms (i.e., both preferred terms and investigator verbatim terms) that could possibly suggest the occurrence of hypotension/orthostatic hypotension or a fall. If a patient experiences any one or more of the various adverse event terms defining the case definition of hypotension/orthostatic hypotension or a fall, the incidence of that adverse event phenomenon is determined.

For adverse events possibly suggestive of a fall, we recommend that you consider the following terms that might be included in this search including: fall, abrasion, laceration, fracture, hematoma (any type), ecchymosis, joint sprain, head injury, and limb injury NOS, and crush injury to a limb. You should consider such events possibly suggestive of a fall unless there is information to suggest that the event was not a result
of a fall. We recommend this minimal list of adverse event terms of how one might analyze for “falls” adverse event terms (e.g. some examples but this is not necessarily a complete list). You can add additional terms to the case definition if you believe they are appropriate.

For adverse events possibly suggestive of hypotension/orthostatic hypotension, we recommend that you consider the following terms that might be included in this search including: blood pressure orthostatic decreased, dizziness postural, orthostatic hypotension, blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, mean arterial pressure decreased, diastolic hypotension, systolic hypotension, hypotension, dizziness, vertigo, light-headedness, postural lightheadedness, impaired balance, and feeling drunk. You should consider such events possibly suggestive of a hypotension/orthostatic hypotension unless there is information to suggest that the event was not a result of hypotension/orthostatic hypotension. The DNP is recommending this minimal list of adverse event terms of how one might analyze for hypotension/orthostatic hypotension adverse event terms (e.g. some examples but this is not necessarily a complete list). You can add additional terms to the case definition if you believe they are appropriate.

Please conduct these analyses for the incidence of adverse events possibly suggestive of falls and of hypotension/orthostatic hypotension for any TEAE, SAEs, TEAEs causing study discontinuation from all time perspectives and also dose perspectives.

Clinical Laboratory Analytes

- Present all outlier analyses for clinical laboratory results showing abnormal results according to whether the result is “low” or “high” based upon whether the result is outside of the “normal” reference range for each laboratory analyte.

- Present all outlier analyses for markedly abnormal clinical laboratory analytes (i.e., markedly decreased/low and markedly increased/high) according to the threshold for markedly abnormally high and low. Recommendations for these markedly abnormal thresholds will be provided with the orthostatic vital sign shells.

- Present all outlier analyses (relative to normal reference range and markedly abnormal thresholds) according to different time perspectives (i.e., abnormal: at any time in trial, during titration period, during maintenance period, “persisting” from titration period into maintenance period, at final visit).

Vital Signs

- We recommend conducting and presenting analyses for central tendency and outliers over time (at every trial visit from baseline until the final trial visit) for orthostatic vital signs (VS) for systolic and diastolic blood pressure and pulse relative to position (i.e., supine, standing, or change from supine to standing) over the whole controlled trial period and over treatment under open-label conditions. In these orthostatic analyses, the supine VS result should be subtracted from the standing VS result (i.e., standing VS result – supine VS result).

- We recommend applying various outlier criteria for orthostatic VS for systolic and diastolic blood pressure and pulse. We are working on completing shells describing and outlining the content and format that we recommend for presenting results of outlier and central tendency analyses. Upon their completion (that is expected within a week), these shells will be provided to you.
• We recommend that you analyze all data for vital sign (VS) outliers according to the VS criteria we have recommended and are providing in the tabular shells for presenting VS analyses. When orthostatic VS measurements have been systematically collected on more than one occasion prior to randomization and initiation of treatment in the baseline/screening period in a trial, it is desirable to average these replicate measurements to serve as the baseline measurement for comparison to all post-treatment measurements.

• Present all outlier analyses according to different time perspectives (i.e., abnormal : at any time in trial, during titration period, during maintenance period, “persisting” from titration period into maintenance period, at final visit).

**ECGs**

• Please conduct analyses of ECG parameters for central tendency and outliers over time similarly as requested for VS in the open-label and controlled trial experience.

• Please present the content and format of ECG data similarly as recommended for presenting results for VS in the tabular shells provided by the division.

• Please provide outlier analyses for these key ECG parameters of interest including:
  
  o QTc (for Bazett and Fridericia correction for all QTc analyses) of > 500, > 480, and > 450 msecs at any time post-baseline/randomization/treatment time

  o QTc change from baseline or change from pre-dosing at > 30 msecs, and > 60 msecs

• Present all outlier analyses (relative to normal reference range and markedly abnormal thresholds) according to different time perspectives (i.e., abnormal : at any time in trial, during titration period, during maintenance period, “persisting” from titration period into maintenance period, at final visit).

**Post-Marketing Experience**

• Please provide a comprehensive integrative review of the post-marketing safety experience globally for safinamide if it has been approved anywhere. Please also pay particular attention to the list of TEAEs of special interest.

**Published Literature**

• Please provide a comprehensive integrative review of the published literature for safinamide. Please also pay particular attention to the list of TEAEs of special interest. Please provide copies of all publications referenced as well as hyperlinks to every publication referenced/discussed in the ISS.
Please include a detailed Table of Contents (TOC) for the ISE with a list of all tables, figures, and listings and ensure the ability to hyperlink to any page shown in the TOC. Please do the same for every report and document in the NDA.

We recommend that you submit shells of the planned efficacy analyses (including all Agency recommended analyses) for review and feedback after reviewing the Agency recommendations. Because many of these analyses will follow the same format, it is not necessary that a shell be presented for each safety analysis when the format is identical. Prototypical shells of all these data can be submitted for review and feedback. Once you have determined the specific format for individual trial and integrated/pooled analyses, we recommend that you submit a list with descriptive names of all tables) of individual safety analyses planned (including all Agency recommended analyses), that would follow specific formats, for DNP review and feedback. Submission of this list for our review will help ensure that you are planning to submit all the efficacy analyses that we want and that we have requested.

Please ensure that the ISE is electronically constructed correctly to show appropriate page coordination in every situation. For example, the page number shown in the table of contents should be the same page number shown on the page after one hyperlinks to that page and when a print command is given to print that page.

The following information outlines and describes efficacy analyses that we are requesting for submission in your NDA. Please contact us if there is any question about deviating from the content and format of efficacy analyses we have requested.

In addition to all the efficacy analyses we are requesting, you are welcome to submit any other efficacy analyses that you deem important.

**Trials**

Conduct all efficacy analyses requested here for the following trials according to the randomized treatment including targeted safinamide dose:

- Study 9 (placebo, 0.5 mg/kg/day, 1.0 mg/kg/day, all safinamide doses)
- Study 15 (placebo, 100 mg, 200 mg, all safinamide doses)
- Study MOTION (placebo, 50 mg, 100 mg, all safinamide doses)
- Study 16 (placebo, 50 mg, 100 mg, all safinamide doses)
- Study SETTLE (placebo, 100 mg)
- Pool of Study 15 and 17 (placebo, 100 mg, 200 mg, all safinamide doses) This analysis considers both of these trials as a single trial.
- Pool of Study MOTION and MOTION EXTENSION (placebo, 50 mg, 100 mg, all safinamide doses) This analysis considers both of these trials as a single trial.
- Pool of Study 16 and 18 (placebo, 50 mg, 100 mg, all safinamide doses) This analysis considers both of these trials as a single trial.

We believe that every patient randomized to receive safinamide was randomized to receive a specific target dose and that titration to that dose was conducted according to the protocol. If there was a problem with tolerability or adverse event(s), the patient could receive a lower safinamide dose. We are
especially interested in analyses according to the randomized, targeted dose. For example, if a patient was randomized to receive 100 mg but was not able to tolerate 100 mg and had to receive a lower dose (e.g., 50 mg), in our desired analysis according to randomized, targeted dose, such a patient would be analyzed in the 100 mg dose group and not in the 50 mg dose group. We are also requesting analyses according to actual dose received based upon the modal dose in a trial.

Please contact the DNP if there are any errors in the above outline of the randomized, targeted doses for each trial.

- For the randomized, double-blinded, controlled trials, we are requesting analytical comparisons of safinamide dose to present all efficacy results for all analyses on the same page according to randomized, treatment (i.e., placebo or safinamide randomized, targeted dose, and all doses).

- Present all efficacy analyses over time. However, it is not necessary to conduct statistical analyses over time. We are interested in statistical analyses conducted at the end of the trial.

- Conduct various sensitivity analyses of all efficacy endpoints

**Efficacy Endpoints**

- Present analyses of all protocol specified efficacy endpoints,

- Please also present analyses for the following endpoints (if the protocol did not specify these endpoints)
  - Change from baseline of UPDRS Part I
  - Change from baseline of UPDRS Part II
  - Change from baseline of UPDRS Part III
  - Change from baseline of UPDRS Part II + III
  - Change from baseline of UPDRS Part I + II + III

- For patients with advanced, Parkinson's disease taking concomitant levodopa and collecting diary data, please analyze all these diary categories for the various change from baseline analysis perspectives outlined below here:
  - “On”
  - “On” with troublesome dyskinesia
  - “On” without troublesome dyskinesia
  - “Off”
  - Sleep

**Change from baseline analysis perspectives for each above outlined diary category:**

- Change from baseline (calculate the change in absolute hours at the end of the trial vs the hours at baseline; e.g., baseline 10 hrs and end of study 12 hrs, change = 12 hrs – 10 hrs = + 2 hrs increase)

- Percentage change from baseline of hours at baseline (calculate absolute change for each diary outcome from absolute parameter/outcome at baseline and express change as a %; e.g.,
baseline 10 hrs and end of study 12 hrs, change = + 2 hrs, 2 hrs change /10 hrs baseline = 20 % increase)

- Change of percentage from baseline (calculate % of each diary outcome at baseline from the absolute hours at baseline and then calculate the % of each diary outcome at the end of the study based upon absolute hours and express the mean change of this %; e.g., 8 hrs at baseline = 33 %, 12 hrs at end of study = 50 %, thus % change from baseline = 50 % - 33 % = + 17 % increase)

**Populations**

- The primary analysis should be for the modified Intent-to-Treat population (mITT) defined as a patient randomized and treated and who had baseline and post-baseline/post-treatment data for the primary efficacy endpoint.

- Observed population: patient randomized and treated and having any post-baseline/post-treatment efficacy data

- Completer population: patient randomized and treated and who completed the trial

**Subgroup Analyses**

- regional subgroups
  - North America vs outside of North America
  - North America vs Western Europe vs all other regions combined (i.e., Eastern Europe, Latin America, Asia, Africa)

- males vs females

- patients > 65 years old vs < 65 years old

- race (for any race with > 5 % of patients)

**Statistical Analyses**

- Conduct statistical analyses as specified in each respective protocol and Statistical Analysis Plan (SAP)

- Conduct analyses using the Mixed Model Repeat Measures (MMRM)

- Conduct analyses according to Last Observation Forward (LOCF)

- Conduct analyses considering rescue treatment administered at the time that data for the final visit efficacy endpoint was collected by adding rescue treatment to the analysis model
APPENDIX II

CLINICAL PHARMACOLOGY SUMMARY

1. Goal

In addition to summarizing the relevant findings the goal of the Clinical Pharmacology Summary is to focus sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions a generic questionnaire is provided that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address.

The Summary generated by sponsors is a stand-alone document, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors’ answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

2. Question Based Review

2.1 List the in vitro and in vivo Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA

All performed Clinical Pharmacology studies (in vitro studies with human biomaterials and in vivo studies) and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple dose, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics
(Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all in vivo studies and indicate corresponding study report numbers.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

2.2.3 What are the proposed dosages and routes of administration?

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects’ demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal t1/2 and AUC.
2.4 Exposure-Response

2.4.1 What are the characteristics of the exposure-response relationship for effectiveness?
Describe briefly the method(s) used to determine the exposure-effectiveness relationship. Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-effectiveness relationship. Provide point estimate as well as a measure of the inter-subject variability for continuous and categorical endpoints. Indicate proportion of responders, if applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, Cmax or Cmin is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

2.4.2 What are the characteristics of the exposure-response relationships for safety?
Describe briefly the method(s) used to determine the exposure-safety relationship. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Of major interest are safety endpoints determining the therapeutic range. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, Cmax or Cmin is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) Cmax and AUC] of the circulating major active
moieties.

Justify if an analysis of the exposure-safety relationship was not done.

2.4.3 Does this drug prolong QT/QTc Interval?
Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc-interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?
Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?
Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [Cmax, tmax, AUC, Cmax,ss, Cmin,ss, Cmax,ss/Cmin,ss, tmax,ss, AUC0-τ, CL/F, V/F and t1/2 (half-life determining accumulation factor), accumulation factor, fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?
Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.
2.5.3 **What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?**
Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, Cmax, Cmin, CL/F and t1/2 of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 **What are the characteristics of drug absorption?**
Indicate absolute bioavailability of drug of parent drug and relative bioavailability, lag time, tmax, tmax,ss, Cmax, Cmax,ss and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

2.5.5 **What are the characteristics of drug distribution?**
Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

2.5.6 **Does the mass balance study suggest renal or hepatic as the major route of elimination?**
Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as metabolites in urine and feces.

2.5.7 **What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?**
Provide identification for ≥ 90% of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivities are too small to be assignable to specific metabolites provide an estimate for their contribution to circulating total radioactivity.

2.5.8 **What are the characteristics of drug metabolism?**
Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance (mL/min) in healthy subjects and patients with the target disease. Indicate whether active metabolites
constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

2.5.9 **Is there evidence for excretion of parent drug and/or metabolites into bile?**
If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

2.5.10 **Is there evidence for enterohepatic recirculation for parent and/or metabolites?**
Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

2.5.10 **What are the characteristics of drug excretion in urine?**
Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

2.5.11 **Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?**
Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) Cmax and AUC values in healthy subjects and patients with the target disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

2.5.12 **How do the PK parameters change with time following chronic dosing?**
Indicate whether the mean ratio of AUC0-τ at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly
from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

2.5.13 **Is there evidence for a circadian rhythm of the PK?**

Indicate whether Cmax and Cmin of the parent drug after the morning and evening dose differ significantly. Discuss the relevance of the findings and whether an adjustment of the dose regimen is required for the drug of interest. Provide a rationale for the underlying mechanism for the observed circadian rhythm of the pharmacokinetics of the drug of interest. Indicate whether the dose regimens in the pivotal studies were adjusted for circadian rhythm.

2.6 **Intrinsic Factors**

2.6.1 **What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?**

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, Cmax, clearance, volume of distribution and t1/2 for pairs studied: elderly vs. young, male vs. female, normal body weight vs. obese, race/ethnicity x vs. race/ethnicity y, mild vs. severe target disease

2.6.2 **Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?**

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (dose or interval) is required or not and provide a rationale for either scenario.

2.6.2.1 **Severity of Disease State**
2.6.2.2 Body Weight

2.6.2.3 Elderly

2.6.2.4 Pediatric Patients
If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

2.6.2.5 Race/Ethnicity

2.6.2.6 Renal Impairment
Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC and Cmax of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, Cmax and CL/F on Clcr for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Indicate mean (SD) for total and renal clearance of the drug in the different sub-groups and provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the sub-groups of patients with impaired renal function and provide a rationale for either scenario.

2.6.2.7 Hepatic Impairment
Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC and Cmax of parent drug and relevant metabolites in the different hepatic function sub-groups assessed...
by two-stage or population PK approaches. Show regressions including 90% confidence intervals of Cmax, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

2.6.2.8 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

2.6.4 Immunogenicity (NOT applicable to small molecule drugs)

2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

2.6.4.3 Do the anti-product antibodies have neutralizing activity?

2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?

2.6.4.5 What is the impact of anti-product antibodies on clinical safety?

Provide information on the incidence of infusion-related reactions, hypersensitivity
reactions, and cross-reactivity to endogenous counterparts.

2.7 Extrinsic Factors

2.7.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?
Summarize the results of the in vitro studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the in vitro results an interaction study in humans is required or is not required.

2.7.2 Is the drug a substrate of CYP enzymes?
Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to Km, controls etc. Provide a summary of the results of the in vitro studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the in vitro findings for the drug of interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?
Briefly describe the methods used (type and source of liver tissue, concentration range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the in vitro studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for Ki, IC50 and Vmax for each relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ([I]). Provide the mean (SD) % activity relative to the positive control for the drug of interest as inducer. Discuss the relevance of the in vitro findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed in vivo in humans. If appropriate use the [I]/Ki ratio as a means to assess the likelihood of an in vitro result to be clinically relevant. For each situation provide supporting evidence.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?
See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of
interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

2.7.5 Are there other metabolic/transporter pathways that may be important?

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?
Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

2.7.7 What are the drug-drug interactions?
Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the in vivo studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report the 90% confidence intervals about the geometric mean ratio for AUC and Cmax for the drug of interest in the presence and absence of each of the co-administered drugs. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report 90% confidence intervals about the geometric mean ratio for AUC and Cmax of each of the co-administered drugs in the presence and absence of the drug of interest.

2.7.8 Does the label specify co-administration of another drug?
2.7.9 What other co-medications are likely to be administered to the target population?

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

2.8 General Biopharmaceutics

For all *in vivo* studies performed in this section indicate study design, demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and Cmax after single and multiple dose administration and peak to trough fluctuation after multiple dose administration.

**IR Product**

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

Indicate composition and calories of the food administered, and length of the pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?

2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product
demonstrated? What is the link between the unapproved/altered and to be marketed products?

MR product (if an IR is already marketed)

2.8.6 What is the bioavailability of the MR product relative to the approved IR product? How does the plasma concentration time profile of the MR formulation compare to that of the IR formulation after single and multiple doses?

Indicate whether or not the pharmacokinetics of the drug of interest is linear, dose proportional or nonlinear after administration of the MR formulation. Summarize data on Cmax, AUC and Cmin of the IR and MR formulations after a single dose and multiple doses at steady-state. Provide information on the fluctuation factor at steady-state.

2.8.7 What is evidence that MR formulation in vivo consistently shows claimed MR characteristics?

2.8.8 What is evidence that MR formulation displays less variability in Cmax, AUC and Cmin than IR formulation?

2.8.9 Does the MR product show dose dumping in vivo?

Describe design, demographics and number of subjects participating in the studies performed to determine whether dose dumping occurs with the MR formulation when given in the fed state or when given together with alcohol. Present summaries of results.

2.8.10 Does ethanol in vitro have a dose-dumping effect on the MR product?

Provide the results of the in vitro dissolution testing of the various strengths of the ER product in pH 1.2, 4.5 and 6.8 media containing 0, 5, 10, 20 and 40% alcohol. Discuss any dose dumping observed. If an in vivo study was performed report the clinical relevance of the findings.

2.8.11 Are the MR and IR products marketed simultaneously?

If the intention is to market both the MR and IR products, indicate how patients are converted from the IR to the MR product and vice versa.

2.8.12 If the NDA is for an MR formulation of an approved IR product without supportive safety and effectiveness studies, what dosing regimen changes are necessary, if any, in the presence or absence
of a PKPD relationship?

2.8.13 In the absence of effectiveness and safety data what data support the NDA for a MR formulation of an approved IR product?

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

List all assays used and briefly describe the individual methods.

2.9.2 Which metabolites have been selected for analysis and why?

2.9.3 For all moieties measured, is free, bound, or total measured?

Indicate whether free, bound or total (bound+unbound) concentrations of the drug of interest and relevant metabolites are measured and give a rationale for your selection.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Identify all studies that used a particular assay method. For each assay report indicate the corresponding assay validation report.

2.8.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

2.9.5.1 What are the lower and upper limits of quantitation?

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).
2.9.5.3 What is the sample stability under conditions used in the study?

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at $\leq -20^\circ$ C.

2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

Applicable to therapeutic proteins only

2.9.5.5 What bioanalytical methods are used to assess therapeutic protein concentrations?

Briefly describe the methods and summarize the assay performance.

2.9.5.6 What bioanalytical methods are used to assess the formation of the anti-product antibodies?

Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

2.9.5.7 What is the performance of the neutralizing assay(s)?
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/s/

ERIC P BASTINGS
10/16/2013
LATE-CYCLE COMMUNICATION DOCUMENTS
Dear Dr. Vogel:

Please refer to your New Drug Application (NDA) dated December 29, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Safinamide Tablets.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 29, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

Gerald D. Podskalny, DO
Clinical Team Lead
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes
MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: September 29, 2015; 1:00-2:00 PM EST
Meeting Location: FDA White Oak: Bldg 22/Room 1309

Application Number: NDA 207145
Product Name: Safinamide Tablets
Applicant Name: Newron Pharmaceuticals

Meeting Chair: Gerald Podskalny, DO, MPHS, CDTL
Meeting Recorder: Stacy Metz, PharmD, RPM

FDA ATTENDEES
Eric Bastings, MD, Deputy Director, DNP
Gerald Podskalny, DO, MPHS, Clinical Team Lead
Len Kapcala, MD, Clinical Reviewer
Alicja Lerner, MD, PhD, CSS Reviewer (via phone)
Xiangmin Zhang, PhD, Statistical Reviewer
Luann McKinney, PhD, Nonclinical Reviewer
Angela Men, PhD, Clin Pharm Team Lead
Kristina Dimova, PhD, Clin Pharm Reviewer
Elisa Braver, OSE/OPE/DEPII
Danielle Harris, OSE/OPE/DEPII
Erin Hachey, OSE/OMERG/DRISK
Stacy Metz, PharmD, Regulatory Project Manager

EASTERN RESEARCH GROUP ATTENDEES
Marc Goldstein, Independent Assessor

APPLICANT ATTENDEES

Consultant
Stephen Graham, PhD, Executive Director, Clinical Development, Newron Pharmaceuticals US
Emma Forrest, PhD, Senior Manager- Clinical Operations, Newron Pharmaceuticals SpA

Statistics Consultant
Statistics Consultant
Toxicology Consultant
Laura Faravelli, PhD, Manager – Preclinical Development, Newron Pharmaceuticals SpA
Daniela Scarcella, Regulatory Affairs Manager, Zambon SpA
Richard Vogel, PhD, Regulatory Affairs Consultant

Reference ID: 3837030
1.0 BACKGROUND

NDA 207145 was submitted on December 29, 2014, for Safinamide Tablets.

Proposed indication(s): Parkinson’s disease

PDUFA goal date: March 29, 2016 (3 month extension)

FDA issued a Background Package in preparation for this meeting on September 16, 2015.

2.0 DISCUSSION

1. Introductory Comments – 5 minutes (Gerald Podskalny, DO, CDTL/Stacy Metz, PharmD, RPM)--Welcome, Introductions, Ground rules, Objectives of the meeting

Discussion:
No further discussion at the meeting.

2. Discussion of Substantive Review Issues – 40 minutes (if needed)

Each issue will be introduced by FDA and followed by a discussion.

- Controlled Substance Staff-Abuse Liability Studies

Discussion:
The sponsor updated the status of the ongoing CSS nonclinical studies. The sponsor estimates they will submit three final nonclinical study reports by the end of November 2015, and a fourth final study report will follow near the end of January 2016.

The CSS reviewer requested the sponsor submit an analysis using the adverse terms provided by the CSS reviewer for signs of abuse, withdrawal and dependence, in the period following discontinuation of safinamide. The previous analysis submitted by the sponsor did not focus on the period following withdrawal from treatment with safinamide. The sponsor agreed to submit the results of this analysis.

- Clinical Team-Issues with the ISS

Discussion:
The sponsor’s submissions and teleconferences to clarify the methods used to reconstruct the population represented in key ISS tables were helpful. Most
of these issues with the ISS have been resolved. The review team will submit an additional information request within a few days of this meeting.

- Clinical and Statistical Teams-Safinamide efficacy for patients with early Parkinson's disease

**Discussion:**
The clinical review team expressed concerns that the clinical trials information provides weak support for safinamide’s effectiveness as adjunctive therapy in patients with early PD, who are taking a stable dose of a dopamine agonist.

Clinical Pharmacology Discussion:
The Clinical Pharmacology reviewer requested the sponsor provide information addressing the potential for drug-drug interactions in humans caused by the inhibitory effect of BCRP by safinamide's major metabolite, NW-1689. The sponsor requested that the Division generate an Information Request on this topic, as Newron has answered a similar request from the EMA; the Clinical Pharmacology reviewer agreed to submit an information request.

3. Discussion of Minor Review Issues

Labeling Discussion

**Discussion:**
Revisions to the label submitted by the sponsor on June 1, 2015, did not permit editing because of formatting problems. The resubmitted label still contains multiple deficiencies because it did not comply with regulation and guidance documents regarding format and content of the label. The sponsor was referred to publically available labels for Rytary and Azilect as examples of recently completed labels for medications approved for the treatment of Parkinson’s disease. The FDA will provide additional edits and comments during labeling negotiations scheduled later in the extended review cycle.

4. Multiple Information Requests – 10 minutes

**Discussion:**
FDA reviewers have needed to send multiple information requests to continue the review of the application to this point. The responses included revision or submission of datasets, guides to identify patients represented in key tables, and additional information about Financial Disclosures. In addition, the Division will send another information request, soon after this meeting. The FDA agrees to review the additional information submitted in response to this information request.
Post Meeting Note:
This information request was finalized and sent October 7, 2015.

5. Review Plans – 5 minutes

The review goal date has been extended to March 29, 2016, to allow for review of your major amendment submitted on August 31, 2015.

Discussion:
No further discussion at the meeting.

6. Wrap-up and Action Items – 5 minutes (Chair will summarize any outstanding action items)

Discussion:
- The sponsor will submit information addressing the potential for drug-drug interaction for the major metabolite of Safinamide, NW-1689.
- The FDA will submit an additional clinical information request soon after this meeting.
- The sponsor will submit a reanalysis of the adverse events related to withdrawal, abuse, and dependency.
- The sponsor and the Division will resolve labeling revisions during labeling negotiations.
- The Division does not anticipate sending Discipline Review letters because review issues have been addressed through information amendments up to this point in the review.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.
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/s/

GERALD D PODSKALNY
10/22/2015