MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 8, 2017

To: Billy Dunn, M.D., Director
Division of Neurology Products

Through: Martin Rusinowitz, M.D., Medical Officer
Silvia Calderon, Ph.D., Pharmacologist
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

(Author: Lerner, Alicja)

AMENDMENT
This memorandum corrects an error and changes the title of Table 4, page 14, in the previously submitted CSS review dated Dec 29, 2016. In our prior review, we erroneously listed the subject population reporting the tabulated adverse events as comprising only healthy volunteers (HV). However, as indicated in the revised Table Title, the data derived from Phase 2 and Phase 3 controlled trials.

This erratum does not change the conclusions or recommendations in the previous CSS review.

Table 4 should read:

Table 4. Summary of Selected Abuse Potential Adverse Events from all Completed Safinamide Phase 2 and Phase 3 Controlled Trials for PD – All Pooled Studies (based on the table 11, page 27, 8 factor-analysis).
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<th>Body System Or Organ Class</th>
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<th>Placebo pool N=919 (n, %)</th>
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<td>Patients with at least one abuse potential event</td>
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- **Nervous system disorders**
  - Somnolence: 79 (5.2) vs 51 (5.5)
  - Dizziness: 87 (5.7) vs 80 (5.4)

- **Psychiatric Disorders**
  - Hallucinations: 47 (3.1) vs 32 (3.5)
  - Mood disorder and disturbances: 7 (0.5) vs 1 (0.1)
  - Psychosis: 4 (0.3) vs 2 (0.2)
  - Confusion and disorientation: 32 (2.1) vs 14 (1.5)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALICJA LERNER
03/08/2017

MARTIN S RUSINOWITZ
03/17/2017

SILVIA N CALDERON
03/17/2017
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ALICJA LERNER
03/08/2017

SILVIA N CALDERON
03/08/2017

MARTIN S RUSINOWITZ
03/09/2017
PMR/PMC Development Template
PMR # 3184-1

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # NDA 207145
Product Name: Xadago (safinamide)

PMR/PMC Description: A clinical trial in healthy volunteers to compare the single-dose pharmacokinetics of a Breast Cancer Resistance Protein (BCRP) substrate, either rosvastatin or sulfasalazine, alone and after administration of multiple doses of safinamide (100 mg/day).

PMR/PMC Schedule Milestones: Final Protocol Submission: 4/30/2017
Study/Trial Completion: 10/31/2017
Final Report Submission: 2/28/2018
Other: MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☐ Theoretical concern
☒ Other

This is appropriate for a PMR because the potential for drug-drug interactions can be described in the prescribing information.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Reference ID: 4065395
NW-1689 is a major metabolite of safinamide found in plasma at a concentration of approximately 160% of the parent compound, safinamide. NW-1689 inhibited BCRP in vitro with an IC₅₀ of 3.7 ± 0.5 μM. The average maximal plasma concentration of safinamide was approximately 4 μM in Parkinson’s disease patients treated with the highest dose of 100 mg/day. Substrates of BCRP include methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosvustatin, sulfasalazine, topotecan. Inhibition of BCRP could increase plasma concentrations of these substrates, resulting in toxicity. The goal of the trial is to evaluate the interaction between safinamide and BCRP substrates in humans.

3. If the study/clinical trial is a PMR, check the applicable regulation. 
   If not a PMR, skip to 4.
   - Which regulation?
     - Accelerated Approval (subpart H/E)
     - Animal Efficacy Rule
     - Pediatric Research Equity Act
     - FDAAA required safety study/clinical trial

   - If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)
     - Asses a known serious risk related to the use of the drug?
     - Assess signals of serious risk related to the use of the drug?
     - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:
     - Analysis of spontaneous postmarketing adverse events?
       - Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
     - Analysis using pharmacovigilance system?
       - Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
     - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       - Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
     - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   A clinical trial in healthy volunteers to compare the single-dose pharmacokinetics of a Breast Cancer Resistance Protein (BCRP) substrate, either rosuvastatin or sulfasalazine, alone and after administration of multiple doses of safinamide (100 mg/day).
5. Is the PMR/PMC clear, feasible, and appropriate?

☐ Does the study/clinical trial meet criteria for PMRs or PMCs?
☐ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed
PMR/PMC Development Coordinator:

☐ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

_______________________________________
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/s/

SALLY U YASUDA
03/06/2017
Date: Dec 29 2016

To: Billy Dunn, M.D., Director
    Division of Neurology Products

Through: Michael Klein, Ph.D., Director
         Controlled Substance Staff

Through: Martin Rusinowitz, M.D., Medical Officer
         Controlled Substance Staff

Through: Silvia Calderon, Ph.D., Pharmacologist
         Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
      Controlled Substance Staff

From: Jovita Randall-Thompson, Ph.D. Pharmacologist
      Controlled Substance Staff

Subject: NDA 207,145/IND 63,901

Name: Safinamide (XADAGO)

Indication: Parkinson’s disease

Dosage: Oral Tablets 50 and 100 mg

Sponsor: Newron Pharmaceuticals SpA

Materials reviewed: NDA submitted Dec 29 2014 and Re-submitted as Class 2 NDA is in EDR
                  09/21/2016
                  PDUFA March 21 2017
                  CSS review Dr. J. Randall-Thompson July 11 2016
                  CSS Review by Dr. A. Lerner March 24 2016
                  CSS Review by Dr. A. Lerner Feb 17 2015
I. SUMMARY

1. BACKGROUND

This memorandum responds to a consultation from the Division of Neurological Products (DNP) to evaluate the abuse potential of safinamide NDA 207,145.

Newron is developing safinamide as adjunctive therapy for the treatment of idiopathic Parkinson’s disease (PD) patients in two identified subpopulations:

- Early stage patients, as add-on therapy to a single DA-agonist at a stable dose.
- Mid- to late-stage patients, as add-on therapy to levodopa (L-dopa) alone or in combination with other PD medications.

Safinamide is a new molecular entity with mechanism of actions that include voltage-gated sodium channel blockade, inhibition of release of glutamate, and selective, reversible inhibition of Monoamine Oxidase B (MAO-B), producing both non-dopaminergic and dopaminergic pharmacological effects. The Sponsor states that safinamide uniquely modulates dopaminergic and non-dopaminergic systems by inhibiting MAO-B, controls neuronal excitability by blocking Na+ channels in a state-dependent manner and inhibits excessive glutamate release.

This is the second NDA submission after receiving refuse-to-file (RTF) for a previous NDA submitted May 29, 2014. The Agency issued the RTF Letter on July 28, 2014, based on organizational and navigational problems in the ISS and ISE sections of the NDA. A CR letter was issued (March 28 2016) due to the absence of nonclinical studies requested by CSS in the 74-day letter.

Safinamide was approved by the European Medicines Agency in February 2015, for the treatment of adult patients with idiopathic Parkinson’s disease as add-on therapy to a stable dose of L-dopa alone or in combination with other Parkinson drugs in patients with mid-to-late-stage disease.
2. CONCLUSIONS

1. Safinamide is a new molecular entity (NME) and has never been marketed in U.S.

2. Safinamide was not found to have abuse potential in the nonclinical studies and the current clinical studies and is, therefore not recommended for scheduling in the Controlled Substances Act (CSA).

3. Non-clinical dependence study showed some withdrawal symptoms. Physical dependence and withdrawal symptoms were not systematically evaluated in humans.
   a. Majority of the studies had only one dedicated follow-up visit at 4 weeks after the taper
   b. Also, there were no relevant withdrawal scales administered to evaluate potential withdrawal syndrome
   c. Both studies Motion and Settle had one week taper of the drug which additionally obscures the withdrawal data, as the taper is currently not indicated in the label
   d. However, the sparse data from clinical trials indicates that there are some withdrawal symptoms.

3. RECOMMENDATIONS

1. The Sponsor should continue to monitor for signs of abuse of the drug and provide the information in periodic post-marketing update reports.

2. Because of the presence of withdrawal symptoms in the nonclinical dependence studies and some withdrawal symptoms noted in the clinical trials, we recommend that a warning be considered in the section 2. DOSAGE AND ADMINISTRATION, 2.1 Dosing Information, such as

   “When discontinuing XADAGO, dosage should be reduced gradually over one week to 10 days.”

3. Additional recommendations for the label:

   In appropriate section of the label, state that safinamide did not show abuse potential in the nonclinical studies. However, observed CNS related adverse events that may relate to abuse potential were mental impairment disorders S: 10 (2.4) vs PL 1 (0.6) in healthy volunteers, and in Parkinson’s patients mood disorders and disturbances [S: 7 (0.5%) vs PL 1 (0.1)], confusion and disorientation [S: 32 (2.1) vs PL 14 (1.5)] and psychotic disorders [S: 4 (0.3) vs PL 2 (0.2)], in LSPD and anxiety [S 13 (1.8) vs PL 6 (1.2)]. Also, a higher frequency of hallucinations was noted in open label studies of 5.2% vs 3.1% during clinical trials.

   In the nonclinical assessment of dependence in rats, safinamide produced some withdrawal symptoms upon discontinuation.
Human dependence and withdrawal were not systematically evaluated. However, the sparse data from the clinical trials indicates that abrupt discontinuation of safinamide, especially in late stage Parkinsonism, may cause worsening of Parkinson’s disease, dyskinesia, cardiovascular disorders such as myocardial infarction and hypotension, psychiatric disorders such as depression, suicidality and hallucinations, falls and eye disorders including scotoma and retinal disorders.

Symptoms of overdose included confusion, sleepiness, forgetfulness, dilated pupils, nausea, vomiting, abdominal pain, increased freezing of legs resulting in falls.

Symptoms of administration of supra-therapeutic doses (greater than 100 mg per day) of safinamide in the clinical trials included headache, dizziness, somnolence, and decreased attention.

II. DISCUSSION - Summary of nonclinical and clinical data related to abuse potential and dependence

Nonclinical abuse potential studies

The current resubmission (Class A) of NDA 201145, safinamide, included Study RS1426, a safinamide drug discrimination assessment with the sedative midazolam. All other nonclinical abuse studies were submitted under the previous NDA submission. The Sponsor submitted Study RS1426 under the current submission. Safinamide at 50 mg/kg and 100 mg/kg was assessed using the drug discrimination procedure in midazolam-trained and d-amphetamine-trained rats (Study RS1426 and Study RS1414) and two drug dependence studies using morphine as a positive control (Study RS1514 and RS1425). In addition, a self-administration study (Study RS1417) was conducted, which evaluated rat response rates of safinamide 0.3, 1 and 1.5 mg/kg per intravenous (i.v.) infusion to the response rates of cocaine.

Nonclinical abuse findings demonstrate a low risk of abuse associated with use of safinamide. Specifically, the established criterion for “no generalization” to midazolam (0.5 mg/kg, IP) and d-amphetamine (0.5 mg/kg, IP), is defined as less than 25% lever-pressing responses on the midazolam lever or d-amphetamine lever. The results for both of the safinamide dose groups did not meet the criterion for generalization to midazolam, mean percentage generalization was 23 ± 27.1% and 14.9 ±20.1%, for the 50 and 100 mg/kg dose groups, respectively. In addition, mean percentage generalization to d-amphetamine was reported at 8.9 ± 6.5% (n = 7) and 18.2 ± 15.7% in the two dose groups, respectively. The self-administration procedure was designed to assess the reinforcing properties of safinamide was not administered at rates comparable to cocaine and was administered at rates only slightly above placebo controls. The dependence study results also demonstrated safinamide effects that were lower than the comparator drug.

Since safinamide has CNS depressant effects, the drug’s lower self-administration rates in comparison to cocaine’s rates could be due to a decrease in general activity. However, the drug discrimination findings with midazolam provide evidence that safinamide’s sedative effects are not rewarding. Taken together, nonclinical abuse-related results indicate that safinamide does not produce relevant levels of stimulant or sedative psychoactive effects, thus signaling that the potential for recreational abuse is unlikely.
A brief description of each study is provided below.

1. **Drug discrimination in Lister Hooded Rats RS1426 and RS1414**

The proposed drug discrimination procedure is designed to evaluate whether a test drug produces physical or psychic perceptions (or interoceptive cues) similar to those produced by a known drug of abuse (e.g., training or reference drug).

**Study RS1426**

The drug discrimination study, RS1426 assessed effects of safinamide (vehicle, 50 and 100 mg/kg (>2x and >4x multiples of human therapeutic Cmax, respectively) given orally (p.o.) and its ability to generalize to the C IV benzodiazepine, midazolam (vehicle and 0.5 mg/kg, i.p./gavage) as the training drug. Alprazolam (C IV), also a benzodiazepine, was used as the procedure control (vehicle and 1.0, 2.0 and 3.0 mg/kg mg/kg, p.o./gavage). Procedure controls are used to show that the training drug was used appropriately. This is established by demonstrating that a drug reported previously to generalize fully to the training drug, generalized fully when tested in the present study. Procedurally, animals were first trained to lever-press once and then up to 5 times for sweetened milk. Next, animals were trained to discriminate the training drug midazolam from vehicle. When injected with midazolam, an animal received milk only when pressing the predetermined lever being paired with midazolam and when injected with vehicle was given access to milk only when pressing the alternate lever, which is consistently paired with vehicle. Once a rat had achieved approximately 60% correct lever-presses on the correct lever on most trials, the ‘testing’ regime was begun. For midazolam verses vehicle testing, on test days rats were injected with midazolam or vehicle and placed in the test chamber for 15 min. This was followed by discriminative testing of safinamide from midazolam and then alprazolam from midazolam, which included rats being placed into the chamber 60 minutes after injection. Each test session lasted 10 minutes. At least 24 hours was used as a washout period between drug treatments.

The methods used were acceptable. As a control, alprazolam generalized to midazolam in a dose-related manner demonstrating that the procedure was effective in evaluating drug discriminative effects. When administered orally, safinamide generalized to saline and evoked no CNS depressant or midazolam-like subjective effects at any of the doses tested.

**Study RS1414**

The drug discrimination study RS1414 was an assessment of safinamide’s (vehicle, 50 and 100 mg/kg given orally, p.o.) ability to generalize to d-amphetamine (C-II) (vehicle and 0.5 mg/kg, i.p./gavage) as the training drug. For this study phentermine (C-IV) was used as a procedure control (vehicle and 1.0, 2.0 and 3.0 mg/kg mg/kg, p.o./gavage). As explained above, procedure controls are used to show that the training drug was used appropriately.
Animals were trained in the same manner as above (see Study RS1426) except that amphetamine was used as the training drug and phentermine was used as the procedural control. Similar to the study above (RS1426), on test days rats were injected with reference drug d-amphetamine or vehicle and placed in the test chamber 15 min later. This was followed by discriminative testing of safinamide from d-amphetamine and phentermine from d-amphetamine, which included rat placement into the chamber 60 minutes after injection. Test sessions were 10 minutes and at least a 24 hours-washout period was used between drug treatments.

For Study RS1414, the methods used were acceptable. However, this study evaluated stimulant interceptive cues. Safinamide is shown to have CNS-depressant activity. As a control, phentermine generalized to amphetamine in a dose-related manner demonstrating that the procedure was effective in evaluating stimulant drug discriminative effects. These findings show that safinamide evoked no stimulant effects and predicts that safinamide will not produce amphetamine-like subjective effects in humans that could relate to stimulant drug abuse.

2. Drug self-administration in Rhesus Monkeys RS1417
The proposed self-administration procedure is designed to assess the reinforcing properties of the drug by evaluating whether the animal will bar press for an infusion of the drug at rates comparable to a training or reference drug.

The self-administration study submitted by the Sponsor assessed vehicle, 0.3, 1.0 and 1.5 mg/kg per i.v. infusion of safinamide. The study subjects were rhesus monkeys (n=4, 2 males and 2 females). All monkeys had a history of lever press training (morphine, cocaine) prior to the current study. Monkeys were surgically implanted with a chronic subcutaneous access port and an indwelling i.v. catheter. Initially, monkeys were trained to reestablish self-administration with cocaine (0.032 mg/kg/injection), on a fixed ratio (FR) 30 schedule (i.e., 30 lever-presses for each infusion of drug). Experiments were conducted in ventilated, sound-attenuating chambers with monkeys seated in chairs, position in front of a panel mounted on the wall on the chamber. In the presence of a green light, after completion of 30 lever presses, a cocaine infusion was delivered followed by a 1 sec presentation of a red stimulus light and a 180 sec time-out period. A minimum of 5 cocaine self-administration sessions were conducted to establish stability of performance, as defined by 3 consecutive sessions in which monkeys received at least 20 infusions of cocaine and the average number of infusions received in each session varied by not more than ± 20%. The ability of safinamide to maintain responding rates at levels comparable to cocaine was assessed. Monkeys were given four sessions of saline between safinamide doses, tested in dosing order of 0.3, 1.0, and then 1.5 mg/infusion (no randomization). All session were 90 minutes in duration.

There were inadequacies reported with study including:
1) Safinamide has CNS depressant properties, thus there is a lack of a justification for the positive control cocaine a stimulant and a sedative procedural control was not assessed.
2) Safinamide Cmax levels were not comparable to human therapeutic Cmax levels.
3) Low sample size.
4) No treatment randomization.

Findings reported include cocaine responding (# of infusions) shown at session mean levels (24.1 ± 1.9) that were significantly (p<0.0001) higher than saline controls (2.3 ± 0.6) and safinamide at 0.3, 1.0, and 1.5 mg/kg per infusion (1.8 ± 0.5, 1.1 ± 0.7 and 2.7 ± 1.5, respectively). However, when comparing safinamide to saline controls, the Sponsor uses each monkey’s individual session means, represented as the number of infusions per session. The Sponsor declared that the highest dose of safinamide, i.e. 1.5 mg/kg/injection, i.v., evoked responding in two of the four monkeys and it appears to serve as a positive reinforcer. It was also specified that the reinforcing effects dissipated on repeated exposure to safinamide. The Sponsor concluded that safinamide has weak positive reinforcing properties.

3. Dependence in Sprague Dawley Rats: Studies RS1514 and RS1425
During safinamide withdrawal, animals showed (at 50 and 100 mg/kg/day) many signs which were present during the treatment, such as hunched posture, stained fur and nose, Straub tail, increased body tone, increased reaction to sound, exophthalmos and piloerection and ataxia. These signs persisted for up to 7 days in spite of T1/2 of 2 hours, which may suggest that some of these signs could have been withdrawal symptoms. In fact, some symptoms were more pronounced during the withdrawal such as increased body tone and ataxia. There were also new symptoms in some animals which for safinamide 50 mg included abnormal posture, teeth chattering, writhing and scratching and for safinamide 100 mg included increased respiration, abnormal posture, and scratching.

4. Receptor Binding and Functional Assays

- Safinamide: 5-HT2A (36%), sigma (75%)[sigma 1 receptor 93%, sigma 2 receptor 85%], Na+ channel (site 2) (67%), NE transporter (46%).
- sigma receptor (50%), norepinephrine transporter (45%), dopamine transporter (64%), Na+ receptor (site 2) antagonist ligand (45%).
- Metabolite NW-1689 AG: mu- opioid receptor (71%), kappa-opioid receptor (41%)
- Metabolite NW-1153-:sigma 1 (85%) agonist ligand

Safinamide has multiple pharmacological mechanisms of actions. Safinamide’s dopaminergic activities include selective reversible inhibition of monoamine oxidase-type B (MAO-B) and monoamine oxidase-type A (MAO-A). It reduces the degradation of dopamine and inhibits dopamine reuptake indicating affinity for the dopamine transporter.

Safinamide also has non-dopaminergic effects, including its ability to act as a glutamate release inhibitor, which causes reduction of induced presynaptic glutamate release in vitro (Marzo et al,
2004\(^1\); Caccia et al, 2006\(^2\); Binda et al, 2007\(^3\) and Final Study Report NW-1015E). It also blocks site 2 of the sodium channel and block calcium channels\(^4\). Activity was seen at micromolar concentrations.

The extent that non-dopaminergic effects contribute to the overall drug effects has not been established.

5. Findings from Safety Pharmacology and Toxicology Studies

1. Irwin test in mice (Study 9750104 (858X))

Safinamide was given to mice at single oral doses of 30, 100, 300 and 1000 mg/kg. At the highest tested dose, safinamide administration was associated with the death of 2 out of 5 mice within 30 minutes after treatment. No delayed mortality was observed up to 7 days after treatment. Starting at 100 mg/kg safinamide caused a dose-related **CNS depression**, such as decreased spontaneous activity and alertness, passivity, loss of righting reflex, reduced muscle tone and grip strength, ataxia, decreased palpebral opening, decreased respiration and dyspnea. These effects lasted up to 6 hours after dosing.

2. Irwin Test in Rats (Study # 11.0016)

The effects of single oral doses of 30, 70 or 200 mg/kg safinamide and 3, 10 or 30 mg/kg on the behavior, autonomic nervous system function, locomotor activity and body temperature were examined in rats for 48 hours after drug administration. Animals received oral placebo, and oral diazepam (8 mg/kg) as the positive control. Safinamide caused slight **dose-dependent CNS depressant effects** (decrease in activity and abdominal muscle tone) associated with mydriasis after oral treatment with 30 to 200 mg/kg. In general, these effects lasted up to 180 minutes after treatment. **Induced weak and transient excitatory and arousing effects** after oral treatment with 3 and 10 mg/kg. At 30 mg/kg, increased reactivity to touch, mydriasis, **increased activity, sniffing and exophthalmia** were seen. These effects also lasted up to 180 minutes after treatment. The positive control diazepam induces CNS depressant effects.

3. Motor Coordination in Mice (Rotarod test) (Study # 9650206)

The possible effect of orally administered safinamide on motor coordination of mice was investigated by measuring the time to stay on a rotating wheel. Safinamide produced motor impairment in the rotarod at relatively high doses, the TD50 of safinamide in the rotarod test was

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\(^4\) Pevarello, P; Bonsignori, A; Caccia, C; Amici, R; Salvati, P; Fariello, RG; McArthur, RA; Varasi, M (1999). "Sodium channel activity and sigma binding of 2-aminopropanamide anticonvulsants". *Bioorganic & Medicinal Chemistry Letters* 9 (17): 2521–2524.
626 mg/kg po. The TD50’s for carbamazepine, phenytoin, valproate, lamotrigine and diazepam were 106, 243, 1178, 84 or 6.8 mg/kg po, respectively.

4. Behavioral study in Rhesus Monkeys (Study # 0907024)
Safinamide, in a range of doses 1 to 10 mg/kg i.m., enhanced the discriminative stimulus of cocaine, but with substantial variability in the potency and time course between monkeys. These results suggest that safinamide pretreatment enhances the discriminative stimulus effects of cocaine in rhesus monkeys. However, the potency and time course of this effect varied substantially among monkeys. One possible source of this individual variability in potency and time course could be individual differences in the distribution and metabolism of CTDP 32,593.

5. Clinical studies

Overview of Exposure to Safinamide in Clinical Studies

The sponsor summarizes the clinical development program as consisting of 37 studies: 20 Phase I, 9 Phase II, and 8 Phase III trials, and included patients in over 20 countries. Four studies which were terminated prematurely by the previous Sponsor: Motion Extension # 27938, OLE # 28850, DAT # 28849, and Study # 024 Cognition.

A total of number of subjects who were enrolled in safinamide studies is 3169; this includes 2539 patients with PD and 572 subjects in nontherapeutic studies, 58 in exploratory therapeutic protocols in Restless Legs Syndrome (RLS) and epilepsy patients before the PD program began.

A total of 2468 subjects received at least one dose of safinamide in clinical trials; 427 subjects were enrolled in non-therapeutic trials, and 2041 patients were enrolled in therapeutic trials, below (Mod. 2.7.4 Overview of Clinical Safety, page 41).

Safinamide Clinical Development Program (based on 2.5 Clinical Overview, page 15)
In the Sponsor’s updated draft 8-Factor analysis in the current submission, an analysis of the abuse potential data using CSS terms for following data pooling was provided:

- Pooled double-blind, placebo-controlled trial patients with early-stage PD (ESPD),
- Pooled double-blind, placebo-controlled trial patients with mid- to late-stage PD (LSPD), and
- Pooled Open-label trial patients.
- A separate analysis for all patients with PD from all completed safinamide Phase 2 and Phase 3 controlled trials.

**Abuse potential in the clinical studies**

The abuse potential related adverse events were relatively infrequent in the clinical trials. In Parkinson’s patients, most frequent AEs were anxiety, restlessness, memory impairment and hallucinations especially in open label studies. In healthy volunteers, most frequent AEs were somnolence and impaired attention, cognition, and psychomotor events.

**Dependence and withdrawal in the clinical studies**

The submitted withdrawal data is deficient because it lacked a systematic evaluation of dependence, withdrawal and rebound.

Also, the data provided as an attempt to evaluate dependence and withdrawal was obtained from a relatively small number of patients many of whom had already gone through a one week taper. However even this sparse and not systematically collected data shows some concerning signals:
<table>
<thead>
<tr>
<th>Body System Or Organ Class</th>
<th>Safinamide pool N=421 (AEs, %)</th>
<th>Placebo pool N=161 (AEs, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of abuse potential cases</td>
<td>36 (8.6)</td>
<td>11 (6.8)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>17 (4)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16 (3.3)</td>
<td>7 (4.3)</td>
</tr>
<tr>
<td>Impaired Attention, Cognition, Mood, and Psychomotor events</td>
<td>21 (5.0)</td>
<td>4 (2.5)</td>
</tr>
</tbody>
</table>

There were very few neuropsychiatric AEs, not unusual for phase 1 study.

**B. Abuse Potential Related Adverse Events in Patients with Early-Stage Parkinson’s Disease (ESPD) with Safinamide as Add-on Drug to a Dopamine Agonist**

This pooling included studies:
- **Study NW-1015/015/III/2003**: A Phase 3, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of 50-100 mg/day and 150-200 mg/day Dose Ranges of Safinamide, as “Add-On” Therapy, in Patients with Early PD Treated with a Stable Dose of a Single DA

- **Study 27918 MOTION**: A Phase III, DB, PL-controlled randomized trial to determine the efficacy and safety of a low (50 mg/day) and high (100 mg/day) dose of Safinamide, as add-on therapy, in subjects with early idiopathic Parkinson’s Disease treated with a stable dose of a single dopamine agonist.

Dopamine agonists included: Pramipexole, Ropinirole, Bromocriptine

For the pooled analysis in patients with ESPD, AEs were reported in Safinamide doses 50/100/200 mg/day patients (N=652), and in placebo patients (N=315).

**Table 2.** Summary of Selected Abuse Potential Adverse Events for Safinamide in ESPD population (N=652) and Placebo (based on Table 13.6.1.1 Treatment-Emergent Adverse Events (TEAE) by Treatment Group Completed Phase 2 and Phase 3 Controlled Trials - Early Stage PD - Studies 015 and MOTION, ISS, page 143)

<table>
<thead>
<tr>
<th>Body System Or Organ Class</th>
<th>ESPD pool</th>
<th>Placebo pool</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=632</td>
<td>N=315</td>
</tr>
<tr>
<td></td>
<td>(AEs, %)</td>
<td>(AEs, %)</td>
</tr>
<tr>
<td><strong>Total no. of cases</strong></td>
<td>427 (67.6)</td>
<td>221 (70.2)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>35 (5.5)</td>
<td>23 (7.3)</td>
</tr>
<tr>
<td>Sedation</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Dizziness</strong></td>
<td>42 (6.3)</td>
<td>18 (5.7)</td>
</tr>
<tr>
<td><strong>Memory impairment</strong></td>
<td>3 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>1 (0.2)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>24 (3.8)</td>
<td>13 (4.1)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>18 (2.8)</td>
<td>8 (2.5)</td>
</tr>
<tr>
<td>Depression/Depressed mood</td>
<td>16 (2.5)</td>
<td>9 (2.9)</td>
</tr>
<tr>
<td>Hallucination /visual</td>
<td>4 (0.7)</td>
<td>6 (1.9)</td>
</tr>
<tr>
<td>Agitation</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Delirium</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Delusion</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Paranoia</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>1 (0.2)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>General Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (2.4)</td>
<td>6 (1.9)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>9 (1.4)</td>
<td>8 (2.5)</td>
</tr>
<tr>
<td><strong>Social Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gambling</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Physical assault</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
</tbody>
</table>

Reference ID: 4035202
*In bold italics* are AEs which are more frequent in safinamide group

**Comment**

Majority of abuse potential related AEs are relatively evenly distributed between safinamide group and placebo. Some noteworthy exceptions are psychiatric disorders delirium, delusion, paranoia and psychotic disorder, but each only once.

**C. Abuse Potential Related Adverse Events in Pooled Group 14 Patients with Late-Stage Parkinson Disease (LSPD)**

This pooling includes following studies:

- **Study 27919 SETTLE**: A Ph III, DB, PL-controlled randomized trial to determine the efficacy and safety of a dose range of 50 to 100 mg/day of Safinamide, as add-on therapy, in subjects with idiopathic PD with motor fluctuations, treated with a stable dose of L-dopa and who may be receiving concomitant treatment with stable doses of a dopamine agonist, an anticholinergic and/or amantadine.

- **Study NW-1015/016/III/2006**: A Ph III, DB, PL-Controlled Study to Determine the Efficacy and Safety of a Low (50 mg/day) and High (100 mg/day) Dose of Safinamide as Add-On Therapy in Pts with Idiopathic PD with Motor Fluctuations, Treated with a Stable Dose of L-dopa and Who May Be Receiving Concomitant Treatment with Stable Doses of a Dopamine Agonist and/or an Anticholinergic

For the Pooled Group 016 and SETTLE patients with LSPD, AEs were reported in a total of 523 (72.5%), all Safinamide patients (N=721), and in 359 (72.2%), placebo patients (N=497).

**Table 3. Summary of selected abuse potential related adverse events in Late Stage PD population for Safinamide doses 50 mg and 100 mg (N=721) and Placebo (N=497) based on ISS Table 14.6.1.1 for LSPD, page 138. Table 14.6.1.1.**

<table>
<thead>
<tr>
<th>Body System Or Organ Class</th>
<th>LSPD pool (N=721) (AEs, %)</th>
<th>Placebo pool (N=497) (AEs, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total no. of cases</strong></td>
<td>523 (72.5)</td>
<td>359 (72.2)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>23 (3.2)</td>
<td>14 (2.8)</td>
</tr>
<tr>
<td>Sedation</td>
<td>1 (0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>21 (2.9)</td>
<td>14 (2.8)</td>
</tr>
<tr>
<td>Amnesia</td>
<td>2 (0.3)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>3 (0.4)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Cognitive disorder</td>
<td>1 (0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>1 (0.1)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>23 (3.2)</td>
<td>12 (2.4)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>13 (1.8)</td>
<td>6 (1.2)</td>
</tr>
</tbody>
</table>
Hallucination /visual 22 (3.0) 18 (3.6)
_Agitation_ 1 (0.1) 0
Depressed mood 3 (0.4) 2 (0.4)
Psychotic disorder 2 (0.3) 2 (0.4)
Hypomania 1 (0.1) 1 (0.2)
Restlessness 2 (0.3) 0
Thinking abnormal 1 (0.1) 0

**General Disorders**
Fatigue 9 (1.2) 13 (2.6)
Asthenia 16 (2.2) 14 (2.8)

*In bold italics* are AEs which are more frequent in safinamide group

**Comments**
Majority of abuse potential related AEs are relatively evenly distributed between safinamide group and placebo. Somnolence, insomnia, and anxiety are higher in the safinamide group, but are not abuse indicating.

In the current submission (Sep 21 2016), the Sponsor pooled adverse events from phase 2 and 3 studies (Table 4).

**Table 4.** NEW. Summary of Selected Abuse Potential Adverse Events for Safinamide in healthy volunteers (HV) population

<table>
<thead>
<tr>
<th>Body System Or Organ Class</th>
<th>All Safinamide pool</th>
<th>Placebo pool</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1516 (n, %)</td>
<td>N=919 (n, %)</td>
</tr>
<tr>
<td>Patients with at least one abuse potential event</td>
<td>230 (15.2)</td>
<td>138 (15)</td>
</tr>
</tbody>
</table>

**Nervous system disorders**
- Somnolence 79 (5.2) 51 (5.5)
- Dizziness 87 (5.7) 80 (5.4)

**Psychiatric Disorders**
- Hallucinations 47 (3.1) 32 (3.5)
- Mood disorder and disturbances 7 (0.5) 1 (0.1)
- Psychosis 4 (0.3) 2 (0.2)
- Confusion and disorientation 32 (2.1) 14 (1.5)

---

**D. Pooled Group 15 Open Label Studies**

Treatment-Emergent Adverse Events (TEAE) by Treatment Group Completed Phase 2 and Phase 3 Controlled Trials - Open-label Studies Targeted Dose
Table 5. Summary of Selected Abuse Potential in ESPD population Adverse Events for Safinamide in ESPD population in Open Label Studies (N=1025) based on Table 15.6.1.1 Treatment-Emergent Adverse Events (TEAE) by Treatment Group Completed Phase 2 and Phase 3 Controlled Trials - Open-label Studies ISS, page 127.

<table>
<thead>
<tr>
<th>Body System Or Organ Class</th>
<th>ESPD pool</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1025</td>
</tr>
<tr>
<td></td>
<td>(AEs, %)</td>
</tr>
</tbody>
</table>

**Total no. of cases**

**Nervous system disorders**
- Somnolence: 16 (1.6)
- Hypersomnia: 4 (0.4)
- Dizziness: 40 (3.9)
- Amnesia: 2 (0.2)
- Memory impairment: 7 (0.7)
- Psychomotor Hyperactivity: 3 (0.3)

**Psychiatric disorders**
- Hallucination/visual/auditory: 53 (5.2)
- Insomnia: 33 (3.2)
- Depression: 25 (2.4)
- Anxiety: 23 (2.2)
- Confusional state: 7 (0.7)
- Delirium: 5 (0.5)
- Delusion/ Delusional dis.: 4 (0.4)
- Aggression: 3 (0.3)
- Agitation: 3 (0.3)
- Restlessness: 4 (0.4)
- Psychotic disorder: 3 (0.3)
- Abnormal behavior: 2 (0.2)
- Suicide attempt: 2 (0.2)
- Completed suicide: 1 (0.1)

**General Disorders**
- Fatigue: 15 (1.5)
- Asthenia: 24 (0.3)

Comments
There is a striking increase in hallucinations to 5.2% not seen in previous poolings. However, there is no placebo group to compare. Other AEs worth mentioning are insomnia, depression, somnolence, anxiety, and psychiatric disorders including delirium, delusion, paranoia and psychotic disorder and suicidality.

4.2 Tolerance and physical dependence studies in humans

In response to 11 February CSS IR, the Sponsor submitted the final available data on withdrawal and dependence for all the TEAE data in the periods ≤2 days, ≤5 days, and ≤30 days OFF.
CSS Consult: NDA 207,145 Safinamide

DRUG, immediately after patients completed the scheduled treatment which included a cumulative data from the following studies:

- Study 009 (for patients not receiving treatment in an open-label extension trial)
- Study 015 (for patients not receiving treatment in Study 017 or in an open-label extension trial)
- Study 017 (for patients not receiving treatment in an open-label extension trial)
- Study MOTION (for patients not receiving treatment in Study MOTION Extension or in an open-label extension trial)
- Study MOTION Extension (for patients completing scheduled treatment or for patients not receiving treatment in an open-label extension trial when they stopped treatment because the trial was stopped)
- Study 016 (for patients not receiving treatment in Study 018 or in an open-label extension trial)
- Study 018 (for patients not receiving treatment in an open-label extension trial)
- Study SETTLE (for patients not receiving treatment in an open-label extension trial)

However, the Sponsor made the following statement, page 1:

“It should be noted that the studies were done at different times over the course of 10 years, and the designs of the studies reflect the different Sponsors and the different regulatory advice received concerning the various protocols; therefore, there are significant differences among the studies in the availability of extension treatment and the safety follow-up that was performed after patients discontinued treatment”

Unfortunately, the data presented is a reflection of this problem, it seems that the only studies which have at all any follow-up data are Motion and Settle. However, these studies had only 1 dedicated follow-up visit at 4 weeks after the taper, also no relevant withdrawal scales were administered to evaluate potential withdrawal syndrome. Also, both studies Motion and Settle had 1 week taper of the drug which additionally obscured the withdrawal data, as the taper is currently not indicated in the label.

The following studies did not have any follow-up safety visit: Study 009, Study 015, Study 016, Study 017, Study 018.

In the studies 016 and 018, patients who discontinued prematurely or who completed treatment period of Week 24 but not entered another study extension completed a 7-day taper period, in which patients on 100 mg safinamide/day had their dose tapered to 50mg/day, and those on 50mg/day received placebo.

Following studies had a dedicated follow-up visit 4 weeks after 1 week taper which included vital signs, ECG, lab tests, AEs, Con Meds:
- MOTION and MOTION Extension study had a one-week taper phase and a dedicated safety follow-up visit 4 weeks later for patients who completed the study and did not enter the MOTION Extension study.
SETTLE study had a one-week taper period and a dedicated safety follow-up visit 4 weeks later.

The following taper schedule was used: the patients on 100mg safinamide/day who did not continue into the OLE, were tapered to 50mg/day for 7 days, while 50mg/day patients received placebo for 7 days.

The analysis of adverse events which occurred during discontinuation period is presented below for the studies which included safety visit 4 weeks after the end of taper (Motion, Settle) and for all other studies which did not include safety visit, and for population of Early Stage Parkinson’s Disease (ESPD) and Late Stage Parkinson’s Disease (LSPD).

1. Withdrawal symptoms in Early Stage Parkinson’s Disease Population

Tables 1A, 1B present the analysis of adverse events reported during discontinuation period for 30 days for the studies 017, Motion Extension, respectively)

**Table 1A.** Adverse events reported during discontinuation period in Study 017 at 30 days

<table>
<thead>
<tr>
<th>Body System Or Organ Class</th>
<th>Safinamide Doses 100 and 200 mg (AEs, %) N=125</th>
<th>Placebo (AEs, %) N=62</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total no. of cases</strong></td>
<td>20 (16)</td>
<td>10 (16)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinson’s disease*</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scotoma</td>
<td>5 (4.0)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Ocular vascular disorder</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Retinal degeneration</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Parkinson’s disease-possibly indicates rebound

**Almost all eye disorders were diagnosed within 2 days after treatment completion.

**Table 1B.** Adverse events reported during discontinuation period in study Motion Extension Study at 30 days.

<table>
<thead>
<tr>
<th>Body System Or Organ Class</th>
<th>Safinamide Doses 100 and 50 mg (AEs, %) N=71</th>
<th>Placebo (AEs, %) N=18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total no. of cases</strong></td>
<td>9 (12.7)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2. Withdrawal Symptoms in Late Stage Parkinson’s Disease Population

Tables 2A, 2B, 2C present the analysis of adverse events reported during discontinuation period of 30 days for the studies 016, 018 and Settle, respectively).

Table 2A. Adverse events reported during discontinuation period in the Study 016 at 30 days.

<table>
<thead>
<tr>
<th>Body System Or Organ Class</th>
<th>Safinamide Doses 100 and 50 mg (AEs, %)</th>
<th>Placebo (AEs, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of cases</td>
<td>7 (25)</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balance disorder*</td>
<td>1 (3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Parkinson’s disease*</td>
<td>1 (3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>1 (3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scotoma</td>
<td>1 (3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Cataract</td>
<td>1 (3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Retinal disorder</td>
<td>1 (3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucinations, visual</td>
<td>1 (3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>1 (3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (3.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Parkinson’s disease and Balance disorder-possibly indicate rebound
Majority of AEs occurred within first 2 days of discontinuation period
Table 2B. Adverse events reported during discontinuation period in the Study 018 at 30 days.

<table>
<thead>
<tr>
<th>Body System Or Organ Class</th>
<th>Safinamide Doses 100 and 50 mg (AEs, %)</th>
<th>Placebo (AEs, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=51</td>
<td></td>
<td>N=28</td>
</tr>
<tr>
<td><strong>Total no. of cases</strong></td>
<td>9 (17.6)</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinson’s disease*</td>
<td>2 (3.9)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinal exudates</td>
<td>1 (2.0)</td>
<td>0</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>2 (3.9)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>1 (2.0)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (2.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Parkinson’s disease -possibly indicates rebound

Table 2C. Adverse events reported during discontinuation period in the Study SETTLE at 30 days.

<table>
<thead>
<tr>
<th>Body System Or Organ Class</th>
<th>Safinamide Doses 100 and 50 mg (AEs, %)</th>
<th>Placebo (AEs, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=20</td>
<td></td>
<td>N=39</td>
</tr>
<tr>
<td><strong>Total no. of cases</strong></td>
<td>2 (10.0)</td>
<td>9 (23.1)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2 (5.0)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (5.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

3. Withdrawal Symptoms Reported During Early Discontinuations

The Sponsor provides the data for adverse events that occurred during 30 days after early drug discontinuation for the study # 016, 015/017 in the population of Early Stage PD and 018 in the population of Early Stage PD.
Table 3. Withdrawal Effects after Early Discontinuation (up to 30 days after Discontinuation) in Completed Phase 2 and Phase 3 Controlled Trials - Early Stage PD - Studies 015/017 based on Table 10.6.1.69 page 5/42 from the sponsor’s response Oct 9 2015.

<table>
<thead>
<tr>
<th>Body System Or Organ Class</th>
<th>Safinamide Doses 100 and 200 mg (AEs, %)</th>
<th>Days OFF Treatment</th>
<th>Placebo (AEs, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ataxia</td>
<td>2 (3.8)</td>
<td>26, 1</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (1.9)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delusions NOT</td>
<td>1 (1.9)</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Hallucinations, visual NOT</td>
<td>1 (1.9)</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4. Selected Withdrawal Effects after Early Discontinuation (up to 30 days after Discontinuation) by Treatment Group Completed Phase 2 and Phase 3 Controlled Trials - Late Stage PD - Studies 016/018 based on Table 12.6.1.69, page 12/42 from the sponsor’s response Oct 9 2015.

<table>
<thead>
<tr>
<th>Body System Or Organ Class</th>
<th>Safinamide Doses 50 and 100 mg (AEs, %)</th>
<th>Days OFF Treatment</th>
<th>Placebo (AEs, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellar infarction</td>
<td>1 (0.8)</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>1 (0.8)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Serotonin syndrome</td>
<td>1 (0.8)</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Cognitive disorder</td>
<td>1 (0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction/Silent MI</td>
<td>3 (2.5)</td>
<td>24, 19, 5</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delusion</td>
<td>1 (0.8)</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Suicidal attempt</td>
<td>1 (0.8)</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>1 (0.8)</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>1 (0.8)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dissociative disorder</td>
<td>1 (0.8)</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>1 (0.8)</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>
Injuries

<table>
<thead>
<tr>
<th>Injury</th>
<th>Count</th>
<th>Specific Dates</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall</td>
<td>4 (3.3)</td>
<td>7, 28, 12, 23</td>
<td>0</td>
</tr>
<tr>
<td>Subdural haematoma</td>
<td>1 (0.8)</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Face injury</td>
<td>1 (0.8)</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

Comments

The reported 30 days early discontinuation adverse events although not too frequent but higher than placebo are concerning, because of their severity. These adverse events included 3 myocardial infarctions; psychiatric events such as suicidality, and psychotic disorder, dissociative disorder, and hallucination. Also, there were neurological disorders such as serotonin syndrome, and stroke (cerebellar infarction/vertebrobasilar insufficiency); there were falls, and related injuries of face and subdural haematoma. This data may suggest that abrupt discontinuation of safinamide causes withdrawal symptoms and the most worrisome ones are cardiovascular and neuropsychiatric.

Clinical pharmacology

Absorption

Safinamide absorption is quite rapid after single and multiple oral dosing, reaching tmax in the time range 1.8-2.8 h after dosing under fasting conditions. Absolute bioavailability is high (approx. 95%) indicating that safinamide is almost completely absorbed after oral administration and that first-pass metabolism is negligible. The high absorption classifies safinamide as a highly permeable drug. Pharmacokinetics of drug was linear both with single dose and repeated dose regimen. Terminal half-life was 21-24 h; steady-state was reached within 5 to 6 days. Food delays the rate of absorption (up to 2 h), without affecting the extent of absorption.

Distribution

The volume of distribution at steady state is 165 L which is 2.3-fold of the body.

Metabolism

In plasma extracts, the main component was parent safinamide, the main circulating metabolite was identified as NW-1689, and 2 minor metabolites, NW-1199 and NW-1153 were identified.

Elimination

The total clearance was determined to be 4.6 L/h classifying safinamide as a low clearance drug. The elimination half-life was in the range of 20-26 h, allowing for once a day administration.

Gender

In several clinical pharmacology studies, PK parameters were compared between sexes. A trend for marginally higher exposure (in terms of Cmax and AUC), and lower CL and Vss for safinamide and its metabolites was observed in females compared to males.

Conclusions

The sponsor’s withdrawal data is deficient because there was no systematic evaluation of dependence, withdrawal and rebound.

Also, the data provided as an attempt to evaluate dependence and withdrawal cannot be considered representative as the data was obtained from a relatively small number of patients.
many of whom had already 1 week taper. However, even this sparse and unsystematically collected data shows some concerning signals:

- Worsening/rebound of Parkinson’s disease, also dyskinesia, ataxia, and balance disorder
- There is a concerning signal for eye disorders in particular scotomas, and retinal disorders which is of importance because retinal pathology was seen in the nonclinical studies.
- Occurrence of cardiovascular AEs such as orthostatic hypotension, hypotension, hypertension, sinus tachycardia and myocardial infarctions.
- Psychiatric disorders such as hallucinations, depression, suicidality

This information should be reflected in the label section 2. Dosage and administration, 2.1 Dosing information and indicate that taper of the drug is needed and also in the section 9.3 Dependence following information will be included.

### 4.3 Overdose

The sponsor states in Mod 2.5.2 that there were two cases of overdose identified, one in the placebo controlled Study 016 (PT ID # 00010150160380004) and one in the OLE extension study 28850 (PT ID # 00000279192520003).

Both overdoses resolved without sequelae.

The first overdose case (PT ID # 00010150160380004) was a female patient who took double the daily dose of study medication for 11 days. Symptoms reported included nausea, increase in freezing of legs while walking, which was associated with falls. Safinamide was temporarily stopped for 1 week and concomitant medication for Parkinson’s disease reduced. All symptoms resolved and the patient continued the randomized therapy.

The second overdose case (with safinamide) was old male patient (PT ID # 00000279192520003) who had a suspected overdose of safinamide, when he decided to withdraw from the study consuming more the daily prescribed dose of 100 mg over a period of one month as judged by drug accountability showing discrepancies, with 22 tablets of 100 mg not returned. The patient experienced symptoms of confusion, sleepiness, forgetfulness and dilated pupils, his other meds included Carbidopa-Levodopa 1125 mg/day, entacapone at a dose of 800 mg/day, and benztropine 7 mg/day. The symptoms resolved on discontinuing medication without sequelae.

### 5. Regulatory Issues and Assessment

**LABEL**

Following changes are proposed to the label: See Recommendations (above).
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/s/

ALICJA LERNER
12/29/2016

MICHAEL KLEIN
12/29/2016
Memorandum

Date: December 23, 2016

To: Eric Bastings, M.D., Deputy Director, Division of Neurology Products (DNP)

Gerald Podskalny, M.D., Team Leader, DNP
Leonard Kapcala, M.D., Medical Officer, DNP

Stacy Metz, Sr. Regulatory Project Manager, DNP

From: Dhara Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD, Team Leader, OPDP

Subject: OPDP draft full Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling comments for XADAGO (safinamide), tablets for oral use

NDA: 207145

On October 11, 2016, DNP consulted OPDP to review the proposed package insert (PI), Patient Package Insert (PPI), and carton and container labeling for XADAGO (safinamide), tablets for oral use (Xadago).

**PI**

OPDP reviewed the version of the draft PI obtained through the DNP Sharepoint on December 21, 2016, and our comments are provided below.

**PPI**

A combined OPDP and Division of Medical Policy Programs (DMPP) patient labeling review was conducted and comments on the PPI were provided under separate cover on December 21, 2016.
**Carton and Container Labeling**

OPDP reviewed the draft carton and container labeling submitted by the Sponsor on December 20, 2016, and accessed on December 22, 2016, through the following eCTD link: `\CDSESUB1\evsprod\NDA207145\207145.enx`.

OPDP has the following comment for labels et-xadago-50mg-30tab, et-xadago-50mg-90tab, et-xadago-100mg-30tab, and et-xadago-100mg-90tab:

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

Thank you for your consult. If you have any questions, please contact Dhara Shah (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

35 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
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/s/

DHARA SHAH
12/23/2016
PATIENT LABELING REVIEW

Date: December 22, 2016

To: Billy Dunn, MD
   Director
   Division of Neurology Products (DNP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
         Associate Director for Patient Labeling
         Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
   Team Leader, Patient Labeling
   Division of Medical Policy Programs (DMPP)

Mathilda Fienkeng, PharmD
   Team Leader
   Office of Prescription Drug Promotion (OPDP)

From: Aman Sarai, BSN, RN
      Patient Labeling Reviewer
      Division of Medical Policy Programs (DMPP)

Dhara Shah, PharmD, RPh
   Regulatory Review Officer
   Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): XADAGO (safinamide)

Dosage Form and Route: Tablets, for oral use

Application Type/Number: 207145

Applicant: Newron Pharmaceuticals SpA
1 INTRODUCTION
On May 29, 2014, Newron Pharmaceuticals SpA submitted for the Agency’s review an original NDA submission in the treatment of Parkinson’s Disease (PD).
Safinamide is a new chemical entity whose mechanism of action includes voltage-gated sodium channel blockade, inhibition of release of glutamate, and selective, reversible inhibition of Monoamine Oxidase B (MAO-B), thus producing both non-dopaminergic and dopaminergic pharmacological effects. Newron has developed safinamide as an adjunctive therapy for the treatment of two subpopulations of idiopathic PD patients: XADAGO (safinamide), tablets for oral use, has a proposed indication for:

- Early stage patients, as add-on therapy to a single DA-agonist at a stable dose.
- Mid-to-late-stage patients, as add-on therapy to L-dopa alone or in combination with other PD medications.

On July 28, 2014, the Agency sent a refusal to file letter to the Applicant stating the application is materially incomplete and sections of the application lack sufficient organization to permit timely, efficient, and complete review by all relevant disciplines.

After several correspondences and meetings, a meeting was held on December 2, 2014 where the Division stated that the organization of the submission was acceptable. On December 29, 2014, the Applicant resubmitting the original NDA application.

On September 16, 2015 the Agency informed the Applicant of a Major Amendment in regards to their August 31, 2015 submission and extended the goal date by three months in order to provide time for a full review of the submission.

On March 29, 2016, the Agency issued a Complete Response letter for this Application citing an unexpected issue identified by the Controlled Substance Staff (CSS) group.

On September 19, 2016 Newron Pharmaceuticals SpA submitted again for the Agency’s review a Class 2 Resubmission for XADAGO (safinamide) in the treatment of Parkinson’s disease.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on October 12, 2016 and October 11, 2016, respectively, for DMPP and OPDP to review the Applicant’s proposed Patient Package Insert (PPI) for XADAGO (safinamide) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft XADAGO (safinamide) PPI received on October 12, 2016, and received by DMPP and OPDP on December 16, 2016.
• Draft XADAGO (safinamide) Prescribing Information (PI) received on October 12, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 16, 2016.

• Approved NEUPRO (rotigotine transdermal system) PPI dated February 26, 2015.

3 REVIEW METHODS
In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:
• simplified wording and clarified concepts where possible
• ensured that the PPI is consistent with the Prescribing Information (PI)
• removed unnecessary or redundant information
• ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
• ensured that the PPI meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS
The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS
• Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
• Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.
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/s/

AMANPREET K SARAI
12/22/2016

DHARA SHAH
12/22/2016

MARCIA B WILLIAMS
12/22/2016
MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: December 21, 2016
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: NDA 207145
Product Name and Strength: Xadago (safinamide) tablets
50 mg, 100 mg
Submission Date: December 20, 2016
Applicant/Sponsor Name: Newron Pharmaceuticals US, Inc.
OSE RCM #: 2014-1249-3
DMEPA Primary Reviewer: Briana Rider, PharmD
DMEPA Team Leader: Lolita White, PharmD

1 PURPOSE OF MEMO
The Division of Neurology Products requested that we review the revised container labels and carton labeling for Xadago (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.a

2 CONCLUSION
The revised container labels and carton labeling for Xadago is acceptable from a medication error perspective. We have no further recommendations at this time.

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Reference ID: 4032195
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/s/

BRIANA B RIDER
12/21/2016

LOLITA G WHITE
12/21/2016
**LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

---

**Date of This Review:** November 18, 2016

**Requesting Office or Division:** Division of Neurology Products

**Application Type and Number:** NDA 207145

**Product Name and Strength:** Xadago (safinamide) tablets
50 mg, 100 mg

**Product Type:** Single Ingredient Product

**Rx or OTC:** Rx

**Applicant/Sponsor Name:** Newron Pharmaceuticals US, Inc.

**Submission Date:** 09/21/2016

**OSE RCM #:** 2014-1249-2

**DMEPA Primary Reviewer:** Briana Rider, PharmD

**DMEPA Team Leader:** Lolita White, PharmD
1 REASON FOR REVIEW

This review evaluates the proposed labels and labeling for Xadago (safinamide) tablets for areas of vulnerability that could lead to medication errors. The Division of Neurology Products (DNP) requested this review as part of their evaluation of NDA 207145 Class 2 Resubmission for Xadago.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B</td>
</tr>
<tr>
<td>Human Factors Study</td>
<td>C-N/A</td>
</tr>
<tr>
<td>ISMP Newsletters</td>
<td>D-N/A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>E-N/A</td>
</tr>
<tr>
<td>Other</td>
<td>F-N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 REGULATORY HISTORY

Newron Pharmaceuticals US, Inc. submitted a 505(b)(1) NDA 207145 on December 29, 2014 for safinamide for the treatment of Parkinson’s disease. The application received a Complete Response on March 28, 2016. The applicant resubmitted NDA 207145 on September 21, 2016, which has been classified as a Class 2 resubmission.

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed Prescribing Information (PI) labeling, container label, carton labeling, and Patient Package Insert (PPI) identified the following areas of needed improvement that may contribute to medication errors:

Prescribing Information (PI)

Our review of the proposed PI notes the following:

1. The administration instructions in Section 2.1 can be clarified to provide consistency throughout the labeling and improve the safe use. Instructions are present in other sections of the labeling but are missing from Section 2.1. Additionally, may
2. Section 16.1 may need to be revised once the Sponsor determines how to differentiate the NDC product codes. Currently, the middle digits of the NDC product codes are sequential (i.e., 110 and 111) which is not an effective differentiating feature. Post-market experience indicates that similarity of the NDC product code numbers has led to selecting and dispensing of the wrong strength.

3. Section 17 under the “Missing Dose” subsection, the statement “Instruct patients to take as XADAGO prescribed” contains a typo which may lead to confusion.

Container Labels and Carton Labeling

2. The colors used to differentiate the product strengths overlap with the colors utilized for the proprietary and nonproprietary names and therefore do not afford adequate differentiation. Additionally, the color contrast between the white container label background and the text of the nonproprietary name and the “X” in Xadago do not afford adequate legibility of the text.

3. Assignment of sequential numbers for the middle digits of the NDC product code numbers is not an effective differentiating feature. The middle 3-4 digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Post-marketing experience indicates that similarity of the NDC product code numbers has led to selecting and dispensing of the wrong strength.

---

*a Metz, S., FDA, March 11, 2016 email to Newron, Safinamide label.
4. The format in which the expiration date will be displayed has not been provided on the draft labeling that was submitted for review. Therefore, we were unable to determine if the expiration date will be clearly labeled and differentiated from the lot number.

We provide recommendations regarding these areas below in Section 5.1 and 5.2 in order to help minimize the potential for medication errors to occur with the use of the product.

5 CONCLUSION & RECOMMENDATIONS

We identified areas in the labels and labeling that are vulnerable to medication error and we recommend revision to provide clarity, increase prominence of critical information and to ensure safe use and storage of the proposed product. We provide recommendations in section 5.1 and 5.2 and recommend their implementation prior to approval of this NDA application.

5.1 RECOMMENDATIONS FOR THE DIVISION

A. Full Prescribing Information
   1. In Section 2.1 Dosing Information:
      a. The administration instructions are not consistent throughout the labeling which may contribute to wrong time errors. Add instructions to administer the dose in the morning to ensure administration instructions are consistent throughout the labeling.
      b. The instructions on what to do if a dose is missed does not explicitly warn against doubling the dose. Add clarification that doses should not be doubled-up if a dose is missed to help mitigate potential extra dose/over dosage errors.
      c. The term may lead to confusion. Revise the statement to minimize the potential for confusion.
   2. In Section 16.1 How Supplied:
      a. Recommendations were provided to the Sponsor in Section 5.2 A3 to address the sequential numbers used for the middle digits of the NDC product codes. Post-marketing experience indicates that similarity of the NDC product code numbers has led to selecting and dispensing of the wrong strength. Coordinate with the Sponsor to determine how they will address recommendation A3 in Section 5.2 below with regards to the NDC product code numbers.
   3. In Section 17 Patient Counseling Information:
      a. The following statement under the “Missing Dose” subsection contains a typo which may lead to confusion. Revise the statement “Instruct patients to take as XADAGO prescribed” to state “Instruct...
patients to take XADAGO as prescribed” to minimize the potential for confusion.

5.2 RECOMMENDATIONS FOR NEWRON PHARMACEUTICALS US, INC.

We recommend the following be implemented prior to approval of this NDA 207145:

A. Container Labels, 50 mg and 100 mg strengths
   1. The colors \( \text{(b)}(4) \) chosen to differentiate the 100 mg and 50 mg strengths overlap with the colors utilized for the proprietary \( \text{(b)}(4) \) and nonproprietary \( \text{(b)}(4) \) names and therefore do not afford adequate differentiation. Additionally, the color contrast between the white container label background and \( \text{(b)}(4) \) text of the nonproprietary name and the “X” in Xadago do not afford adequate legibility of the text. (See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors; April 2013). Revise the labels to maximize the legibility of the nonproprietary name and ensure adequate differentiation between the product strengths.

   2. Assignment of sequential numbers for the middle digits of the NDC product code numbers (i.e., 110 and 111) is not an effective differentiating feature. Post-marketing experience indicates that similarity of the NDC product code numbers has led to selecting and dispensing of the wrong strength. The middle 3-4 digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Please revise the middle digits so they are not sequential. If for some reason the middle digits cannot be revised, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type. For example: XXXX-XXXX-XX

B. Carton Labeling, 50 mg and 100 mg strengths
   1. See A.1, A.2, and A.3.

\(^b\) Metz, S., FDA, March 11, 2016 email to Newron, Safinamide label.
2. We note the “serialization area” will contain the 2D barcode, Lot #, Expiration Date, GTIN and Serialization number. Post-marketing experience indicates that errors have occurred when the lot number and expiration date were not clearly labeled or differentiated. Ensure that the lot number and expiration date are clearly labeled and differentiated from one another. Consider labeling the lot number and expiration date in a manner similar to the format presented on the container label to minimize the potential for confusion.

C. Professional Sample Carton Labeling, 50 mg and 100 mg strengths
   1. See A.1, A.2, and A.3.

D. Professional Sample Blister Labels, 50 mg and 100 mg strengths
   1. The placeholder for the expiration date does not indicate the expiration date format that you intend to use. Post-marketing experience indicates that errors have occurred when the expiration date was not clearly labeled or differentiated from the lot number. Please provide the intended expiration date format for evaluation.

---


APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xadago that Newron Pharmaceuticals US, Inc. submitted on September 21, 2016.

<table>
<thead>
<tr>
<th>Table 2. Relevant Product Information for Xadago (safinamide)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Approval Date</strong></td>
</tr>
<tr>
<td><strong>Active Ingredient</strong></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
</tr>
<tr>
<td><strong>Dosage Form</strong></td>
</tr>
<tr>
<td><strong>Strength</strong></td>
</tr>
<tr>
<td><strong>Dose and Frequency</strong></td>
</tr>
<tr>
<td><strong>How Supplied</strong></td>
</tr>
<tr>
<td><strong>Storage</strong></td>
</tr>
<tr>
<td><strong>Container Closure</strong></td>
</tr>
</tbody>
</table>
APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On October 13, we searched the L:drive and AIMS using the terms, Xadago and Safinamide to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews\(^{e,f}\) and we confirmed that our previous recommendations were implemented or considered.

On August 28, 2015 DMEPA performed its first review (OSE RPM #2014-1249)\(^e\) of the proposed labels and labeling for Xadago tablets for areas of vulnerability that could lead to medication errors. DMEPA provided the Sponsor with several recommendations to provide clarity, increase prominence of critical information and help ensure safe use and storage of the proposed product.

On March 17, 2016 DMEPA reviewed (OSE RCM #2014-1249-1)\(^f\) the revised container and carton labeling for Xadago that were submitted in response to recommendations made during previous label and labeling reviews.\(^{e,f}\) DMEPA found that the Applicant satisfactorily revised the labels and labeling and no further recommendations were made at that time.

\(^{e}\) Harris, D. Label and Labeling Review for Xadago (safinamide) (NDA 207145). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 AUG 28. RCM No.: 2014-1249.

\(^{f}\) Harris, J. Review of Revised Label and Labeling for Xadago (safinamide) (NDA 207145). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAR 17. RCM No.: 2014-1249-1.

\(^{g}\) Metz, S. FDA, March 8, 2016 email to Newron, DMEPA recommendations for the revised container labels and carton labeling submitted January 11, 2016.
G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Xadago labels and labeling submitted by Newron Pharmaceuticals US, Inc. on September 21, 2016.

- Professional Sample Blistercards
- Professional Sample Carton Labeling
- Container labels
- Carton labeling
- Full Prescribing Information (no image)
- Medication Guide (no image)

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/s/

BRIANA B RIDER
11/18/2016

LOLITA G WHITE
11/18/2016

Reference ID: 4015884
MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 24, 2016
To: Billy Dunn, M.D., Director
Division of Neurology Products
Through: Michael Klein, Ph.D., Director
Controlled Substance Staff
From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff
From Jovita Randall-Thompson, Ph.D. Pharmacologist
Controlled Substance Staff

Subject: NDA 207,145/IND 63,901
Name: Safinamide (XADAGO)
Indication: Adjunctive treatment for Parkinson’s disease patients experiencing “off” episodes while receiving concomitant levodopa with or without other dopaminergic medications
Dosage: Oral tablets 50 and 100 mg
Sponsor: Newron Pharmaceuticals SpA

Materials reviewed: Re-submitted NDA 207,145 is in EDR, Dec 29 2014
Extended PDUFA, March 29 2016
Review CSS by Dr. Alicja Lerner, Feb 17 2015

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I. BACKGROUND

This memorandum responds to a consult request from the Division of Neurological Products (DNP) to evaluate the abuse potential of safinamide NDA 207,145. Newron is developing
Safinamide as adjunctive therapy for the treatment of idiopathic Parkinson’s disease (PD) patients in two identified subpopulations:

- Early stage patients, as add-on therapy to a single DA-agonist at a stable dose.
- Mid- to late-stage patients, as add-on therapy to L-dopa alone or in combination with other PD medications.

Safinamide is a new molecular entity, with mechanism of actions that include also voltage-gated sodium channel blockade, inhibition of release of glutamate, and selective reversible inhibition of Monoamine Oxidase B (MAO-B), producing both non-dopaminergic and dopaminergic pharmacological effects. The Sponsor states that safinamide uniquely modulates dopaminergic and non-dopaminergic systems by inhibiting MAO-B, controls neuronal excitability by blocking Na\(^+\) channels in a state-dependent manner and inhibits excessive glutamate release.

Of note, this is the second NDA submission after Refuse-to-file (RTF) for a previous NDA submitted May 29, 2014. The Agency issued an RTF Letter on July 28, 2014, because of organizational and navigational problems in the ISS and ISE sections of the NDA.

The Sponsor provided the Agency, on August 25, 2015, a list of the abuse studies they were going to submit, delineated below, and on November 2, 2015 provided time estimates on when each study would be submitted, as follows:

- a drug discrimination study with amphetamine as the training drug (March 2016)
- a drug discrimination study with midazolam as the training drug (April 2016)
- a self-administration study with cocaine as the training drug (January 2016), and
- two dependence studies (December 2015)

However, the first study report arrived only on January 22, 2016, and the last one still to be submitted on April 15, 2016, is after goal PDUFA date.

The current NDA submission includes an assessment of the abuse and dependence-related adverse events reported during clinical testing and post-marketing, and all of the above mentioned pre-clinical studies with the exception of the pivotal drug discrimination study with the prototypical sedative midazolam used as the training drug.

II. CONCLUSIONS (to be conveyed to Sponsor)

1. Safinamide has never been marketed in the U.S. As a new molecular entity (NME) that is CNS active there is sufficient reason that safinamide may have abuse potential which needs to be evaluated. Safinamide actions include voltage-gated sodium channel blockade, inhibition of release of glutamate, and selective reversible inhibition of Monoamine Oxidase B (MAO-B), producing both non-dopaminergic and dopaminergic pharmacological effects.

2. The pre-clinical drug discrimination study (Study RS1414) using amphetamine as the training drug indicates that the interceptive cues produced by safinamide are weakly
similar to the interceptive cues induced by the stimulant, amphetamine. However, this assessment is designed to assess if safinamide produces effects that are similar to the effects produced by a stimulant. Since safinamide produces sedative/depressant effects, a discrimination test using a sedative/depressant agent is needed to further characterize safinamide’s effects. The Sponsor was not able to submit Study RS1426 by the PDUFA date. Study RS1426 included an assessment of the interceptive cues of safinamide in comparison to the interceptive cues of the CNS depressant, midazolam.

3. The pre-clinical self-administration study (Study RS1417) has significant methodological deficiencies:
   a. Inappropriate positive control/ does not include a CNS depressant as a positive control
   b. Too high of a fixed ratio response schedule (FR-30) as CNS depressants produce lower levels of responding
   c. No treatment exposure randomization
   d. Low number of subjects (4 primates)
   e. The tested low doses do not produce Cmax levels comparable to the Cmax levels of human therapeutic doses
   f. Study was designed only to test safinamide for stimulant effects

4. Although the self-administration study has significant deficiencies, the Sponsor declared that the highest dose of safinamide, i.e. 1.5 mg/kg/injection IV evoked responding in two of the four monkeys (50% of subject tested) and it appears to serve as a positive reinforcer. The Sponsor concluded that safinamide appears to have some weak positive reinforcing properties.

5. In the clinical studies, the following AEs were reported by healthy subjects: somnolence, decreased attention, dizziness, and fatigue, and the patients with Parkinson’s disease reported: insomnia, anxiety, restlessness somnolence, and memory impairment, occasional delirium, delusion, and paranoia. In an open label study, PD patients showed increased incidence of hallucinations, suicidality, insomnia, confusional state, delirium and restlessness. Hallucinations and CNS depression show a possible abuse potential signal.

6. The clinical dependence and withdrawal data submitted by the Sponsor is insufficient because there was no systematic evaluation of dependence, withdrawal and rebound:
   a. Majority of the studies submitted by the Sponsor did not have any follow-up visit to evaluate dependence
   b. Only 2 studies MOTION and SETTLE had only one follow-up-visit at 4 weeks after 1 week of taper
   c. No relevant scales such as depression scale, sleepiness scale, physician withdrawal checklist, stimulant withdrawal scale, and UPDRS were used to assess withdrawal and rebound
   d. The only 2 studies which had a follow-up visit had also 1 week taper which obscures any potential evaluation of withdrawal
e. A general paucity of any adverse events during the discontinuation period for the submitted studies is striking.

f. However, even this sparse and very poorly collected data shows some concerning signals:
   o Possible rebound of Parkinson’s disease including hypokinesia and balance disorder
   o Possible concerning signal for eye disorders in particular scotomas, and retinal disorders which is of importance because of retinal pathology seen in animal studies
   o Possible cardiovascular AEs such as orthostatic hypotension, hypotension, hypertension, sinus tachycardia
   o The data from Early Discontinuations may suggest that abrupt discontinuation of safinamide causes withdrawal symptoms and the most worrisome ones are cardiovascular adverse events (myocardial infarctions, cardio-respiratory arrests) and neuropsychiatric (suicidality), injuries due to falls and deaths.

g. Therefore, a dedicated evaluation of clinical dependence, withdrawal and rebound is requested as PMR.

III. RECOMMENDATIONS (to be conveyed to Sponsor)

1. The Sponsor should follow through with the submission of the additional preclinical study with midazolam as the training drug/comparator.

2. The Sponsor should conduct a human abuse potential study (HAPS).

3. Evaluation of dependence and withdrawal is requested; however, it can be performed as PMR. The evaluation of dependence and rebound in patients with Parkinson's Disease can be performed at the end of a future clinical trial in Parkinson’s Disease patients or as an independent dependency study in PD patients. The duration of discontinuation period should be at least 3 weeks from the drug discontinuation and will include reports of adverse events and of disease-specific scales administered at the last day of study, then biweekly using the following measures:
   o Unified Parkinson’s Disease Rating Scale (UPDRS)
   o Dopamine Dysregulation Syndrome-Patient and Caregiver Inventory (DDS-PC, Cabrini et al., 2009)\(^1\)
   o Depression Scale
   o Sleepiness Scale
   o Stimulant withdrawal scale (Amphetamine Withdrawal Questionnaire, AWQ, or Cocaine Selective Severity Assessment, CSSA)
   o Physicians Withdrawal Checklist (PWC)

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Reference ID: 3907536
4. CSS invites the Sponsor to submit protocols prior to conducting the studies which we will review and provide comments to the Sponsor.
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/s/

ALICJA LERNER
03/24/2016

JOVITA F RANDALL-THOMPSON
03/24/2016

MICHAEL KLEIN
03/24/2016
Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date: March 22, 2016

To: Billy Dunn, MD
   Director
   Division of Neurology Products (DNP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
   Associate Director for Patient Labeling
   Division of Medical Policy Programs (DMPP)

   Shawna Hutchins, MPH, BSN, RN
   Team Leader, Patient Labeling
   Division of Medical Policy Programs (DMPP)

   Mathilda Fienkeng, PharmD
   Team Leader
   Office of Prescription Drug Promotion (OPDP)

From: Aman Sarai, BSN, RN
   Patient Labeling Reviewer
   Division of Medical Policy Programs (DMPP)

   Aline Moukhtara, RN, MPH
   Regulatory Review Officer
   Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): XADAGO (safinamide)

Dosage Form and Route: Tablets, for oral use

Application Type/Number: 207145

Applicant: Newron Pharmaceuticals SpA
1 INTRODUCTION

On May 29, 2014, Newron Pharmaceuticals SpA submitted for the Agency’s review an original NDA submission in the treatment of Parkinson’s Disease (PD). Safinamide is a new chemical entity whose mechanism of action includes voltage-gated sodium channel blockade, inhibition of release of glutamate, and selective, reversible inhibition of Monoamine Oxidase B (MAO-B), thus producing both non-dopaminergic and dopaminergic pharmacological effects. Newron has developed safinamide as an adjunctive therapy for the treatment of two subpopulations of idiopathic PD patients: XADAGO (safinamide), tablets for oral use, has a proposed indication for:

- Early stage patients, as add-on therapy to a single DA-agonist at a stable dose.
- Mid-to-late-stage patients, as add-on therapy to L-dopa alone or in combination with other PD medications.

On July 28, 2014, the Agency sent a refusal to file letter to the Applicant stating the application is materially incomplete and sections of the application lack sufficient organization to permit timely, efficient, and complete review by all relevant disciplines.

After several correspondences and meetings, a meeting was held on December 2, 2014 where the Division stated that the organization of the submission was acceptable. On December 29, 2014, the Applicant resubmitting the original NDA application.

On September 16, 2015 the Agency informed the Applicant of a Major Amendment in regards to their August 31, 2015 submission and extended the goal date by three months in order to provide time for a full review of the submission.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on March 4, 2015 and March 3, 2015, respectively, for DMPP and OPDP to review the Applicant’s proposed Patient Package Insert (PPI) for XADAGO (safinamide) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft XADAGO (safinamide) PPI received on March 16, 2016, and received by DMPP and OPDP on March 16, 2016.
- Draft XADAGO (safinamide) Prescribing Information (PI) received on May 29, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 16, 2016.
• Approved NEUPRO (rotigotine transdermal system) PPI dated February 26, 2015.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:
• simplified wording and clarified concepts where possible
• ensured that the PPI is consistent with the Prescribing Information (PI)
• removed unnecessary or redundant information
• ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
• ensured that the PPI meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

• Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

• Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.
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/s/

AMANPREET K SARAI  
03/22/2016

ALINE M MOUKHTARA  
03/22/2016

SHAWNA L HUTCHINS  
03/22/2016

LASHAWN M GRIFFITHS  
03/22/2016
On March 3, 2015, DNP consulted OPDP to review the proposed package insert (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for XADAGO (safinamide) tablets, for oral use (Xadago).

**PI**

OPDP reviewed the substantially completed version of the draft PI obtained through the DNP Sharepoint on March 18, 2016. Our comments are provided directly on the marked version below.

**Carton and Container Labeling**

OPDP has reviewed the attached draft version of the carton and container labeling submitted by Newron Pharmaceuticals on March 11, 2016, and obtained through DARRTS/EDR.

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

**PPI**

The Division of Medical Policy Programs (DMPP) and OPDP will provide comments on the draft PPI under a separate cover.

If you have any questions, please contact Aline Moukhtara (301) 796-2841 or Aline.Moukhtara@fda.hhs.gov.
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/s/

ALINE M MOUKHTARA
03/21/2016
MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: March 17, 2016
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: NDA 207145
Product Name and Strength: Xadago (safinamide) tablets
50 mg, 100 mg
Submission Date: March 11, 2016
Applicant/Sponsor Name: Newron Pharmaceuticals
OSE RCM #: 2014-1249-1
DMEPA Primary Reviewer: Justine Harris, RPh
DMEPA Team Leader: Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO
The Division of Neurology Products (DNP) requested that we review the revised container label and carton labeling for Xadago (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.¹ ²

2 CONCLUSION
The revised container label and carton labeling for Xadago is acceptable from a medication error perspective. We have no further recommendations at this time.

¹ Harris D. Label and Labeling Review for XADAGO (NDA 207145). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 AUG 28. 11 p. OSE RCM No.: 2014-1249.
² Metz, S., FDA, March 8, 2016 email to Newron, DMEPA recommendations for the revised container labels and carton labeling submitted January 11, 2016.
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/s/

JUSTINE HARRIS
03/17/2016

DANIELLE M HARRIS
03/17/2016
MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: Dec 1, 2015

To: Billy Dunn, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: NDA 207145/IND 63901
Name: Safinamide
Indication: Parkinson’s disease
Dosage: Oral Tablets 50 and 100 mg
Sponsor: Newron Pharmaceuticals SpA

Materials reviewed:
Re-submitted NDA is in EDR Dec 29 2014
Discontinuation adverse events Oct 16 2015, Sequence Number 045
Extended PDUFA March 29 2016

I. BACKGROUND
This memorandum responds to a consult request from the Division of Neurological Products (DNP) to evaluate the abuse potential of Safinamide NDA 207,145.

II. CONCLUSION
At CSS’ request, the Sponsor submitted on Oct 16 2015, Sequence Number 045, data on adverse events that occurred during the discontinuation period.

III. RECOMMENDATIONS
The data raises multiple questions. The Sponsor needs to clarify or provide responses to the following issues:
1. The meaning of the “early discontinuation” in the context of the sentence below, page 1. Does it mean that all early discontinuations were due to AEs or withdrawal of consent or both, or other reasons?

All adverse events that occurred following early discontinuation from the early stage Parkinson’s disease (ESPD) studies 015/017 and late stage Parkinson’s disease (LSPD) Studies 016/018 were tabulated according to whether they occurred up to 2 days, 5 days and 30 days following discontinuation

2. Reasons for the early discontinuation.

3. The length of time the patients were followed after they discontinued from the study, whether there were hospitalizations, and other outcome of these AEs

4. Serious adverse events occurring during the discontinuation period.

5. How the patients were evaluated during the discontinuation period, such as, was it as a follow-up visit or by phone call. Or was it just one evaluation following early discontinuation? Were the follow up visits on 2nd, 5th and 30th day scheduled for each patient in this population?

6. Were the early discontinued patients evaluated only once at the time when they discontinued or was there any follow up visit/phone call during the 30 days of discontinuation period.

7. There seems to be a significant difference up to 4 times between duration of discontinuation of AEs in safinamide group vs placebo group. Were these adverse events serious adverse events? Did they resolve? What was the outcome? It seems that safinamide administration resulted in much higher toxicity as expressed by mean duration of AEs.

8. Were Unified Parkinson’s Disease Rating Scale (UPDRS) scores obtained during the discontinuation period for patients in early and late phase PD studies, there seem to be more neurological AEs in safinamide group particularly in late stage PD study

9. Were the adverse events in patients who completed the full treatment phase in early and late phase PD studies also evaluated during discontinuation period?
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/s/

ALICJA LERNER
12/01/2015

MICHAEL KLEIN
12/01/2015
### LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

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<th>August 28, 2015</th>
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<td>Division of Neurology Products (DNP)</td>
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<td><strong>Application Type and Number:</strong></td>
<td>NDA 207145</td>
</tr>
<tr>
<td><strong>Product Name and Strength:</strong></td>
<td>Xadago (safinamide) tablets</td>
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<td></td>
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<td><strong>Product Type:</strong></td>
<td>Single Ingredient Product</td>
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<td><strong>Rx or OTC:</strong></td>
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<tr>
<td><strong>Applicant/Sponsor Name:</strong></td>
<td>Newron Pharmaceuticals</td>
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<tr>
<td><strong>Submission Date:</strong></td>
<td>December 29, 2014</td>
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<td><strong>OSE RCM #:</strong></td>
<td>2014-1249</td>
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<tr>
<td><strong>DMEPA Primary Reviewer:</strong></td>
<td>Danielle Harris, PharmD, BCPS</td>
</tr>
<tr>
<td><strong>DMEPA Associate Director:</strong></td>
<td>Irene Z. Chan, PharmD, BCPS</td>
</tr>
</tbody>
</table>
1 REASON FOR REVIEW
This review evaluates the proposed labels and labeling for Xadago (safinamide) tablets for areas of vulnerability that could lead to medication errors. The Division of Neurology Products (DNP) requested this review as part of their evaluation of NDA 207145 for Xadago.

2 MATERIALS REVIEWED
We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
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<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B</td>
</tr>
<tr>
<td>Human Factors Study</td>
<td>C – N/A</td>
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<td>ISMP Newsletters</td>
<td>D – N/A</td>
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<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>E – N/A</td>
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<tr>
<td>Other</td>
<td>F – N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
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</table>

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED
Our review of the prescribing information identified areas of vulnerability from a medication error perspective.

The intended route of administration does not appear in Section 11 Description and should be added to comply with 21 CFR 201.57 (c)(12)(B).

In Section 14.1, we note the presence of trailing zeros to denote dosing regimens (i.e., “1.0 mg/kg/day”) used in clinical trials and are concerned that this information could be misinterpreted. Numbers containing decimal points can lead to tenfold dosing error when the decimal point goes unseen. To minimize such errors, trailing zeros should not be used to express information related to dosage.

Section 16 How Supplied lists (b)(4). These packaging configurations should be removed.
Our review of the container label and carton labeling identified areas of vulnerability from a medication error perspective. The established name on the trade container labels and professional sample carton labeling lacks prominence and does not appear to be at least half the size of the proprietary name. The established name should be revised in accordance with 21 CFR 201.10(g)(2).

The statement of strength on the trade container labels and professional sample carton labeling lacks prominence due to the small font size and text color. Additionally, there is inadequate differentiation between the 50 mg and 100 mg strengths. The statement of strength should be revised to ensure this critical information is prominent and additional strategies should be employed to differentiate between the 50 mg and 100 mg strengths to prevent errors related to product selection. Additionally, the net quantity statement is located in close proximity to, and competes in prominence with, the statement of strength. This should be revised to mitigate the potential for confusion between the strength and the net quantity.

The current temperature statements do not contain the temperature scale designation (i.e., “C” or “F) after each numerical value. We are concerned that this information could be misinterpreted and should therefore be revised for clarity.

The salt equivalency statement is distracting and contributes to clutter on the principle display panel (PDP). The statement should be relocated to the side panel to ensure the statement does not detract from the critical information on the PDP.

To mitigate the potential for patient confusion, the statement of strength on the blister pack carton labeling could be revised to clearly indicate the dose per individual unit (i.e., XX mg per tablet). Additionally, the text of the strength printed on the blister labels is small and difficult to read and should be increased in size, if space permits.

4  CONCLUSION & RECOMMENDATIONS
We have identified areas in the labels and labeling that are vulnerable to medication error and we recommend revision to provide clarity, increase prominence of critical information and help ensure safe use and storage of the proposed product. We provide recommendations in section 4.1 and 4.2 and recommend their implementation prior to approval of this NDA application.
4.1 RECOMMENDATIONS FOR THE DIVISION

1. Full Prescribing Information
   a. Add the intended route of administration to Section 11 Description to comply with 21 CFR 201.57 (c)(12)(B).
   b. Remove trailing zeros from the dosing regimens in Section 14.1 to prevent misinterpretation of information related to studied doses.
   c. Remove the 14-count physician sample blister packs from Section 16.1 as these presentations are not intended for sale.

4.2 RECOMMENDATIONS FOR THE NEWRON PHARMACEUTICALS

We recommend the following be implemented prior to approval of this NDA 207145:

1. Trade Container Labels, 50 mg and 100 mg strengths
   a. The established name lacks prominence and does not appear to be at least half the size of the proprietary name. Increase the font size of the established name in accordance with 21 CFR 201.10(g)(2).
   b. The statement of strength lacks prominence due to the small font size and text color. Increase the prominence of this critical information by means of bolding, increasing font size, boxing, color, or other means [21 CFR 201.15(a)(6)].
   c. There is inadequate differentiation between the 50 mg and 100 mg strengths. To prevent medication errors related to product selection, revise the presentations of the strengths using boxing, color differentiation, or other means, to provide adequate differentiation. (See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors; April 2013). If you choose to use color to differentiate the strengths, ensure the colors chosen are unique and do not overlap with any other colors utilized in the labeling.
   d. To avoid confusion with the statement of strength, ensure the net quantity statement (i.e., 30 tablets) is not located in close proximity to, and does not compete in prominence with, the statement of strength. Post-marketing experience indicates that the risk of confusion increases when the strength and net quantity are in close proximity.
f. Revise the temperature statements to include the C or F after each number (i.e., 15°C-30°C (59°F –86°F)) for clarity.

g. Relocate the statement “Each tablet contains XX mg safinamide (as safinamide mesylate)” to the side panel to ensure the statement does not detract from the critical information on the Principal Display Panel.

2. Professional Sample Carton Labeling, 50 mg and 100 mg strengths
   a. See 1.a., 1.b., 1.c., 1.d., 1.e., 1.f., and 1.g.
   b. Consider revising the statement of strength on the blister carton labeling to read “XX mg per tablet” to prevent patient confusion as to how much product is contained in a single blister unit as compared to the total blister card.

3. Professional Sample Blister Labels, 50 mg and 100 mg strengths
   a. If space permits, increase the size of the tablet strength text.
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xadago (safinamide) tablets that Newron Pharmaceuticals submitted on March 30, 2015.

<table>
<thead>
<tr>
<th>Table 2. Relevant Product Information for Xadago (safinamide)</th>
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<tbody>
<tr>
<td><strong>Initial Approval Date</strong></td>
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<td><strong>Active Ingredient</strong></td>
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| **Indication** | 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. |
| **Route of Administration** | Oral |
| **Dosage Form** | Tablet |
| **Strength** | 50 mg, 100 mg |
| **Dose and Frequency** | 50 mg or 100 mg once daily |
| **How Supplied** | 30 and 90 count bottles and 14-count professional sample blisters |
| **Storage** | Store at 25°C; excursions permitted between 15°C and 30°C (59°F to 86°F)[See USP controlled room temperature] |
| **Container Closure** | The bottles are HDPE sealed with closures  
  The blister film foil is composed of |
APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods
On April 1, 2015, we searched the L:drive and AIMS using the terms, “Xadago” to identify reviews previously performed by DMEPA.

B.2 Results
Our search did not identify any previous relevant reviews.
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Xadago (safinamide) labels labeling submitted by Newron Pharmaceuticals on March 30, 2015 (carton, container and blister) and August 11, 2015 (PI).

- Trade Container labels
- Professional Sample Blister Labels
- Professional Sample Carton Labeling
- Prescribing Information (no image)


3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
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/s/

DANIELLE M HARRIS
08/28/2015

IRENE Z CHAN
08/30/2015
CLINICAL INSPECTION SUMMARY

DATE: August 14, 2015

TO: Stacy Metz, Pharm.D., Regulatory Health Project Manager
Leonard Kapcalia, M. D., Medical Officer
Division of Neurology Products

FROM: Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader for
Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 207145

APPLICANT: Newron Pharmaceuticals USA, Inc.

DRUG: Xadago (safinamide mesylate)

NME: No

THERAPEUTIC CLASSIFICATION: Standard
INDICATION: Treatment of patients with Idiopathic Parkinson’s disease
CONSULTATION REQUEST DATE: February 27, 2015
DIVISION ACTION GOAL DATE: December 29, 2015
PDUFA DATE: December 29, 2015
INSPECTION SUMMARY: October 1, 2015
I. BACKGROUND:

The Applicant has conducted two studies in support of approval of safinamide in the treatment of subjects with idiopathic Parkinson’s disease (PD). Parkinson’s disease is an idiopathic neuro-degenerative disorder characterized clinically by tremor, rigidity, akinsea, and loss of postural reflexes. Anatomically, lesions affect mainly dopaminergic neurons in the substantia nigra. These lesions result in a deficit of dopamine in the neostriatum, particularly the putamen. Although this condition is generally not fatal nor life shortening, it causes major disability and are extremely difficult to prevent at later –stages of the disease.

Safinamide, known as propanamide methanesulfonate, is an alpha aminoamide derivative. Safinamide possesses multiple mechanism of action that may be of benefit in the treatment of patients with PD, as well as other CNS disorders, e.g. Epilepsy, Alzheimer’s disease, Dementia and Restless Legs Syndrome. The mechanisms of action include blockade of voltage and use-dependent sodium channels, and calcium channels modulation, inhibition of glutamate release, and modulation of dopaminergic metabolism through selective, reversible inhibition of monoamine oxidase-B. Safinamide is not approved in the U.S. The Applicant has developed the drug product for consumers who suffer from Idiopathic Parkinson’s Disease with motor fluctuations, treated with stable dose of levodopa and who may be receiving concomitant medications with stable doses of dopamine agonist.

The Applicant-sponsored two clinical trials NW-1015/016 and NW-1015/018 in support of the application: the trials are the same with the exception that study 018 is a long-term extension of study 016.

Protocols: NW-1015/016: “A Phase III, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of a Low Dose (50 mg/day and High (100 mg/day) Dose of Safinamide, as ADD-ON Therapy, in Patients with Idiopathic Parkinson’s With Motor Fluctuations, Treated with a Stable Dose of Levodopa and Who May be Receiving Concomitant Treatment with Stable Doses of A Dopamine Agonist, and or An Anticholinergic” and

NW-1015/016: “A Phase III, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of a Low Dose (50 mg/day and High (100 mg/day) Dose of Safinamide, as ADD-ON Therapy, in Patients with Idiopathic Parkinson’s With Motor Fluctuations, Treated with a Stable Dose of Levodopa and Who May be Receiving Concomitant Treatment with Stable Doses of A Dopamine Agonist, and or An Anticholinergic”.

These protocols are essentially the same; therefore a single description of the key design features is presented below.

Protocols NW-1015/016 & NW-1015/018

The study was a double-blind, placebo-controlled, parallel group, randomized, multicenter,
multinational, phase III trial, comparing two doses of safinamide (50 and 100 mg/day, p.o.) versus placebo as add-on therapy to a stable dose of levodopa in Parkinson’s disease patients with motor fluctuations. The trials enrolled approximately 18 patients per center in approximately 30 sites in India, 5 sites in Italy, and 10 sites in Romania. The study duration was 108 weeks, including the screening period (10 days), a levodopa stabilization phase (4 weeks), the treatment period (24 weeks), and the extension period (78 weeks). Eligible subjects received treatment with safinamide or placebo for a total of 102 weeks (24 weeks initial treatment plus 78-week extension treatment). All randomized subjects completing their participation in the double-blind treatment period in Study (016) were enrolled in a 78 week, double blind extension Study NW-1015/018 protocol.

The objective of this study was to evaluate the efficacy and safety of two doses of safinamide (50 and 100 mg/day, p.o.), compared to placebo, as add-on- therapy in patients with idiopathic Parkinson’s disease with motor fluctuations, who were currently receiving a stable dose of levodopa.

The primary efficacy objective was an increase in mean daily “on” time without dyskinesia plus “on” time with minor dyskinesia during 18-hr diary recording period.

The Division of Neurology Products (DNP) requested inspection of the following clinical investigator sites due to high subject enrollment.

II. RESULTS (by protocol/site):

<table>
<thead>
<tr>
<th>Name of CI, Site #, and Location</th>
<th>Protocol and # of Subjects</th>
<th>Inspection Dates</th>
<th>Final Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rupam Borgohain, M.D. Punjap, Hyderabad India Site#016</td>
<td>Protocols1015/016 &amp;1015/018 39 and 33 subjects</td>
<td>6/1-5/2015</td>
<td>NAI</td>
</tr>
<tr>
<td>Jozsef Szasz, M.D. Mures, Romania 540136 Site# 071</td>
<td>Protocols1015/016 &amp; 1015/018 39&amp;34 subjects</td>
<td>5/11-15/2015</td>
<td>VAI</td>
</tr>
</tbody>
</table>

Key to Classifications
NAI = No deviations
VAI = Deviation(s) from regulations
OAI = Significant deviations for regulations. Data generated are unreliable.
Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

1. Rupam Borgohain, M.D.
Punjaguta, Hyderabad 500082, India

   a. What Was Inspected: For Protocol NW-1015/016, a total of 51 subjects were screened, 12 subjects were reported as screen failures, 39 subjects were enrolled,
and 34 subjects completed the study. For protocol NW-1015/018 a total of 33 subjects continued on the extension phase of the study, and 28 subjects completed the study. Review of the Informed Consent Documents, for all records reviewed, verified that subjects signed prior to enrollment.

A review of the medical records/source documents was conducted. The medical records for 14 subjects enrolled in protocol NW-1015/15 and 13 subjects enrolled in protocol NW-1015/018 were reviewed, including drug accountability records, protocol deviations, vital signs, laboratory test results, IRB records, inclusion/exclusion criteria, financial disclosure, and concomitant medications. Source documents were compared to data listings, including primary efficacy endpoints and adverse events.

b. General Observations/Commentary: Our investigation found no evidence of under reporting of adverse events. No significant violations were noted and a Form FDA 483 was not issued. Minor record keeping violations were noted in terms of “documents were not filed properly in the regulatory binders such as training certification, financial disclosure, and IRB and CRO correspondence. The ORA investigator reported that the subject binders were falling apart and were out of order, and not all study coordinators signed Financial Disclosure Forms prior to, during or after the closure of the study”

The medical records reviewed disclosed no adverse findings that would reflect on the reliability/acceptability of the data. In general, the records reviewed were adequate and the data verifiable except for the above noted findings. There were no known limitations to this inspection.

c. Assessment of Data Integrity
Although minor deviations were noted, the data generated by this site are considered reliable and appear acceptable in support of the pending application.

2. Joszsef Szasz, M.D., Ph.D.
Mures, 540136, Romania

a. What Was Inspected: At this site, a total of 45 subjects were screened, eight subjects were reported as screen failure, 37 subjects were enrolled into the study, and 37 subjects completed studies; all 37 subjects continued on the extension phase of the Study 1015/018. Two subjects withdrew from the extension phase of the study, and thirty five subjects completed Study 1015/018. Review of the Informed Consent Documents, for all records reviewed, verified that subjects signed prior to enrollment.

The medical records/source data for 10 subjects from Study1015/016, and 16 subjects from Study 101/018 were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB records, patients’ diaries for inclusion/exclusion criteria, concomitant medications, and source documents were compared to data listings and adverse events reporting.

b. General Observations/Commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Szasz. The medical records reviewed disclosed no
adverse findings that would impact the reliability of data. However, the ORA investigation found minor protocol deviations and inadequate record keeping. The inspectional observations discussed with clinical investigator included, but were not limited to the following:

**Protocol violations.**

1. According to the protocol, signed informed consents had to be signed by the subjects prior to any study procedures. The ORA investigator reported that during the 1015/018 study, Subjects #71008 and 71009 did not have a signed informed consent (version #4) document on site as being done/obtained prior to study procedures.

**Inadequate record keeping.**

2. The drug accountability records were incomplete and did not include an explanation for lost product and products never received or returned by subjects to the clinical site. Subjects did not return study drug after a visit and it was reported as lost in the drug accountability records. The ORA investigators were not able to verify how much drug was dispensed and returned by each subject.

3. Subject # 71025 received Amlodipine during study 1015/016. The use of concomitant medication was not recorded on the concomitant medication page of the case report form.

4. During study 1015/016 numerous obliteration of data were found on the source documents. The clinical investigator stated that this was his first study and since that time he learned to cross out errors with a single line, initial and date. The ORA investigator noticed that on later study records errors were corrected with a single line, initialed and dated.

5. The study coordinator, [REDACTED] the ophthalmologist who took part in the study should have been listed on the Delegation Log or on your Statement of Investigator Form FDA-1572 as a person responsible to you.

The clinical investigator verbally acknowledged the inspectional observations in which he agreed with the observations and stated that he will address the discussed findings in his future studies. OSI finds his verbal response acceptable.

The medical records reviewed disclosed no adverse findings that would impact the reliability of the data. In general, the records reviewed were found to be in order except for the above noted findings. There were no limitations to this inspection.

c. **Assessment if Data Integrity:** Although minor deviations were noted, the data from Dr. Szasz’s site are considered reliable and appear acceptable in support of the pending application.
III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Two foreign clinical investigators were inspected in support of this application. The inspections of Dr. Szasz revealed minor deviations that would not adversely impact data acceptability. The final classification for Dr. Szasz is Voluntary Action Indicated (VAI), and the final classification for Dr. Borgohain is No Action Indicated (NAI). Overall the data submitted from the two sites are acceptable and may be used in support of the pending application.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader for
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Division of Clinical Compliance Evaluation
Office of Scientific Investigations
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANTOINE N EL HAGE
08/18/2015

SUSAN D THOMPSON
08/18/2015

Reference ID: 3807526
1. Regulatory History and Applicant’s Main Proposals

Safinamide is a new chemical entity whose mechanism of action includes voltage-gated sodium channel blockade, inhibition of release of glutamate, and selective, reversible inhibition of Monoamine Oxidase B (MAO-B), thus producing both non-dopaminergic and dopaminergic pharmacological effects. Newron has developed safinamide as adjunctive therapy for the treatment of two subpopulations of idiopathic Parkinson’s disease (PD) patients:

- Early stage patients, as add-on therapy to a single DA-agonist at a stable dose.
- Mid- to late-stage patients, as add-on therapy to L-dopa alone or in combination with other PD medications.

Two Pre-NDA meetings with FDA were held in 2013: (1) on August 29th with ONDQA and DNP to discuss CMC issues (Sponsor Minutes (SN 276, 9/6/13), 9/27/13 FDA minutes, and (2) on September 16th with DNP to discuss nonclinical, clinical pharmacology and clinical issues (Sponsor Minutes (SN 280, 10/1/13), 10/16/13 FDA minutes. The NDA was submitted on May 29th 2014. The Agency subsequently issued an NDA Refusal to File (RTF) Letter July 28th.

2. Review of the Prescribing Information

This review is based on the applicant’s submitted Word format of the prescribing information (PI). The applicant’s proposed PI was reviewed in accordance with the labeling format requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by March 29, 2015. The resubmitted PI will be used for further labeling review.
Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

<table>
<thead>
<tr>
<th>YES</th>
<th>1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comment:</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.</td>
</tr>
<tr>
<td>Comment:</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.</td>
</tr>
<tr>
<td>Comment:</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>4. All headings in HL must be bolded and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.</td>
</tr>
<tr>
<td>Comment:</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.</td>
</tr>
<tr>
<td>Comment:</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.</td>
</tr>
<tr>
<td>Comment:</td>
<td></td>
</tr>
</tbody>
</table>
| YES  | 7. Section headings must be presented in the following order in HL:

<table>
<thead>
<tr>
<th>Section</th>
<th>Required/Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highlights Heading</td>
<td>Required</td>
</tr>
<tr>
<td>Highlights Limitation Statement</td>
<td>Required</td>
</tr>
<tr>
<td>Product Title</td>
<td>Required</td>
</tr>
</tbody>
</table>
Selected Requirements of Prescribing Information

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Initial U.S. Approval</td>
<td>Required</td>
</tr>
<tr>
<td>• Boxed Warning</td>
<td>Required if a BOXED WARNING is in the FPI</td>
</tr>
<tr>
<td>• Recent Major Changes</td>
<td>Required for only certain changes to PI*</td>
</tr>
<tr>
<td>• Indications and Usage</td>
<td>Required</td>
</tr>
<tr>
<td>• Dosage and Administration</td>
<td>Required</td>
</tr>
<tr>
<td>• Dosage Forms and Strengths</td>
<td>Required</td>
</tr>
<tr>
<td>• Contraindications</td>
<td>Required (if no contraindications must state “None.”)</td>
</tr>
<tr>
<td>• Warnings and Precautions</td>
<td>Not required by regulation, but should be present</td>
</tr>
<tr>
<td>• Adverse Reactions</td>
<td>Required</td>
</tr>
<tr>
<td>• Drug Interactions</td>
<td>Optional</td>
</tr>
<tr>
<td>• Use in Specific Populations</td>
<td>Optional</td>
</tr>
<tr>
<td>• Patient Counseling Information Statement</td>
<td>Required</td>
</tr>
<tr>
<td>• Revision Date</td>
<td>Required</td>
</tr>
</tbody>
</table>

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all **UPPER CASE** letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in **UPPER CASE** letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in **UPPER CASE**, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.
Selected Requirements of Prescribing Information

Comment:

N/A 14. The BW must always have the verbatim statement “See full prescribing information for complete boxed warning.” This statement should be centered immediately beneath the heading and appear in italics.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “See full prescribing information for complete boxed warning.”).

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

NO
21. All contraindications listed in the FPI must also be listed in 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 HL: Hypersensitivity to the active substance or to any of the excipients [see DESCRIPTION (11)].*

**Adverse Reactions in Highlights**

**YES** 22. 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:*
*Sponsor needs to update (TBD).*

**Patient Counseling Information Statement in Highlights**

**YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:
- “See 17 for PATIENT COUNSELING INFORMATION”

If a product **has** FDA-approved patient labeling:
- “See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling”
- “See 17 for PATIENT COUNSELING INFORMATION and Medication Guide”

*Comment:*

**Revision Date in Highlights**

**YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “Revised: 9/2013”).

*Comment:*
Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: “FULL PRESCRIBING INFORMATION: CONTENTS”. This heading should be in all UPPER CASE letters and bolded.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and bolded.

Comment:

YES 28. In the TOC, all section headings must be bolded and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”

Comment:
Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in **UPPER CASE** and **title case**, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<table>
<thead>
<tr>
<th>BOXED WARNING</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 INDICATIONS AND USAGE</td>
</tr>
<tr>
<td>2 DOSAGE AND ADMINISTRATION</td>
</tr>
<tr>
<td>3 DOSAGE FORMS AND STRENGTHS</td>
</tr>
<tr>
<td>4 CONTRAINDICATIONS</td>
</tr>
<tr>
<td>5 WARNINGS AND PRECAUTIONS</td>
</tr>
<tr>
<td>6 ADVERSE REACTIONS</td>
</tr>
<tr>
<td>7 DRUG INTERACTIONS</td>
</tr>
<tr>
<td>8 USE IN SPECIFIC POPULATIONS</td>
</tr>
<tr>
<td>8.1 Pregnancy</td>
</tr>
<tr>
<td>8.2 Labor and Delivery</td>
</tr>
<tr>
<td>8.3 Nursing Mothers</td>
</tr>
<tr>
<td>8.4 Pediatric Use</td>
</tr>
<tr>
<td>8.5 Geriatric Use</td>
</tr>
<tr>
<td>9 DRUG ABUSE AND DEPENDENCE</td>
</tr>
<tr>
<td>9.1 Controlled Substance</td>
</tr>
<tr>
<td>9.2 Abuse</td>
</tr>
<tr>
<td>9.3 Dependence</td>
</tr>
<tr>
<td>10 OVERDOSE</td>
</tr>
<tr>
<td>11 DESCRIPTION</td>
</tr>
<tr>
<td>12 CLINICAL PHARMACOLOGY</td>
</tr>
<tr>
<td>12.1 Mechanism of Action</td>
</tr>
<tr>
<td>12.2 Pharmacodynamics</td>
</tr>
<tr>
<td>12.3 Pharmacokinetics</td>
</tr>
<tr>
<td>12.4 Microbiology (by guidance)</td>
</tr>
<tr>
<td>12.5 Pharmacogenomics (by guidance)</td>
</tr>
<tr>
<td>13 NONCLINICAL TOXICOLOGY</td>
</tr>
<tr>
<td>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</td>
</tr>
<tr>
<td>13.2 Animal Toxicology and/or Pharmacology</td>
</tr>
<tr>
<td>14 CLINICAL STUDIES</td>
</tr>
<tr>
<td>15 REFERENCES</td>
</tr>
<tr>
<td>16 HOW SUPPLIED/STORAGE AND HANDLING</td>
</tr>
<tr>
<td>17 PATIENT COUNSELING INFORMATION</td>
</tr>
</tbody>
</table>

**Comment:**

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see Warnings and Precautions (5.2)]” or “[see Warnings and Precautions (5.2)]”.

**Comment:**
Selected Requirements of Prescribing Information

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be *bolded* and appear at the beginning of the FPI: “FULL PRESCRIBING INFORMATION”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be *bolded*.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word “WARNING” (even if more than one Warning, the term, “WARNING” and not “WARNINGS” should be used) and other words to identify the subject of the Warning (e.g., “WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”).

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and
Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:
Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME] (nonproprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

• [text]

--- RECENT MAJOR CHANGES ---

[section (X,Y)] [m/year]
[section (X,Y)] [m/year]

--- INDICATIONS AND USAGE ---
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

--- DOSAGE AND ADMINISTRATION ---

• [text]

• [text]

--- DOSAGE FORMS AND STRENGTHS ---

--- CONTRAINDICATIONS ---

--- WARNINGS AND PRECAUTIONS ---

--- ADVERSE REACTIONS ---

Most common adverse reactions (incidence > 5%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

--- DRUG INTERACTIONS ---

--- USE IN SPECIFIC POPULATIONS ---

--- PATIENT COUNSELING INFORMATION ---

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

1 WARNING: [SUBJECT OF WARNING]
2 INDICATIONS AND USAGE
   2.1 [text]
   2.2 [text]
3 DOSAGE AND ADMINISTRATION
   3.1 [text]
   3.2 [text]
4 DOSAGE FORMS AND STRENGTHS
5 CONTRAINDICATIONS
6 WARNINGS AND PRECAUTIONS
   5.1 [text]
   5.2 [text]
7 ADVERSE REACTIONS
   6.1 [text]
   6.2 [text]
8 DRUG INTERACTIONS
   7.1 [text]
   7.2 [text]
9 DRUG ABUSE AND DEPENDENCE
   9.1 Controlled Substance
   9.2 Abuse
   9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
   12.1 Mechanism of Action
   12.2 Pharmacodynamics
   12.3 Pharmacokinetics
   12.4 Microbiology
   12.5 Pharmacogenetics
13 NONCLINICAL TOXICOLOGY
   13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
   13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
   14.1 [text]
   14.2 [text]
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
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
03/06/2015
RPM FILING REVIEW
(Including Memo of Filing Meeting)
To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

<table>
<thead>
<tr>
<th>Application Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA # 207145</td>
</tr>
<tr>
<td>BLA#</td>
</tr>
<tr>
<td>NDA Supplement #: S-</td>
</tr>
<tr>
<td>BLA Supplement #</td>
</tr>
<tr>
<td>Efficacy Supplement Type SE-</td>
</tr>
<tr>
<td>Proprietary Name:</td>
</tr>
<tr>
<td>Established/Proper Name: Safinamide mesylate</td>
</tr>
<tr>
<td>Dosage Form: oral tablet</td>
</tr>
<tr>
<td>Strengths: 50mg and 100mg</td>
</tr>
<tr>
<td>Applicant: Newron Pharmaceuticals, S.p.A.</td>
</tr>
<tr>
<td>Agent for Applicant (if applicable): [Redacted]</td>
</tr>
<tr>
<td>Date of Application: May 27, 2014</td>
</tr>
<tr>
<td>Date of Receipt: May 29, 2014</td>
</tr>
<tr>
<td>Date clock started after UN: [Redacted]</td>
</tr>
<tr>
<td>PDUFA Goal Date: May 29, 2015</td>
</tr>
<tr>
<td>Action Goal Date (if different):</td>
</tr>
<tr>
<td>Filing Date: July 28, 2014</td>
</tr>
<tr>
<td>Date of Filing Meeting: July 10, 2014</td>
</tr>
<tr>
<td>Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1</td>
</tr>
<tr>
<td>Proposed indication(s)/Proposed change(s): • early stage, patients being treated with a single dopamine agonist at a stable dose</td>
</tr>
<tr>
<td>• mid- to late stage patients receiving L-dopa and other PD treatments</td>
</tr>
<tr>
<td>Type of Original NDA: AND (if applicable)</td>
</tr>
<tr>
<td>Type of NDA Supplement: [X] 505(b)(1)</td>
</tr>
<tr>
<td>[ ] 505(b)(2)</td>
</tr>
<tr>
<td>[ ] 505(b)(3)</td>
</tr>
<tr>
<td>[X] 505(b)(4)</td>
</tr>
<tr>
<td>If 505(b)(2): Draft the “505(b)(2) Assessment” review found at: [Link]</td>
</tr>
<tr>
<td>Type of BLA</td>
</tr>
<tr>
<td>If 351(b), notify the OND Therapeutic Biologics and Biosimilars Team</td>
</tr>
<tr>
<td>Review Classification: [X] Standard</td>
</tr>
<tr>
<td>[ ] Priority</td>
</tr>
<tr>
<td>[ ] Tropical Disease Priority Review Voucher submitted</td>
</tr>
<tr>
<td>[ ] Pediatric Rare Disease Priority Review Voucher submitted</td>
</tr>
<tr>
<td>Resubmission after withdrawal?</td>
</tr>
<tr>
<td>Resubmission after refuse to file?</td>
</tr>
<tr>
<td>Part 3 Combination Product? [ ]</td>
</tr>
<tr>
<td>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consents</td>
</tr>
<tr>
<td>[ ] Convenience kit/Co-package</td>
</tr>
<tr>
<td>[ ] Pre-filled drug delivery device/system (syringe, patch, etc.)</td>
</tr>
<tr>
<td>[ ] Pre-filled biologic delivery device/system (syringe, patch, etc.)</td>
</tr>
<tr>
<td>[ ] Device coated/impregnated/combined with drug</td>
</tr>
<tr>
<td>[ ] Device coated/impregnated/combined with biologic</td>
</tr>
<tr>
<td>[ ] Separates products requiring cross-labeling</td>
</tr>
<tr>
<td>[ ] Drug/Biologic</td>
</tr>
<tr>
<td>[ ] Possible combination based on cross-labeling of separate products</td>
</tr>
<tr>
<td>[ ] Other (drug/device/biologic product)</td>
</tr>
</tbody>
</table>

Version: 4/15/2014
Reference ID: 3604946
<table>
<thead>
<tr>
<th>Goal Dates/Product Names/Classification Properties</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDUFA and Action Goal dates correct in tracking system?</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td>Product name was listed as (b)(4) dosage form correct as tablets, corrected product name to &quot;safinamidé&quot; 7.21.14</td>
</tr>
<tr>
<td>Are the proprietary, established/proper, and applicant names correct in tracking system?</td>
<td>☐</td>
<td>☒</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov/9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov/9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

**Application Integrity Policy**

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></td>
<td>☐</td>
<td>☒</td>
<td>☐</td>
<td>List checked 7.21.14</td>
</tr>
</tbody>
</table>

If yes, explain in comment column.

If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified: ☐ ☐ ☐

**User Fees**

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is Form 3397 (User Fee Cover Sheet) included with authorized signature?</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td>Small business waiver granted for original submission submitted before January 27, 2015</td>
</tr>
</tbody>
</table>
User Fee Status

If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.

Payment for this application:

☐ Paid
☒ Exempt (orphan, government)
☐ Waived (e.g., small business, public health)
☐ Not required

Payment of other user fees:

☐ Not in arrears (as of July 15, 2014 list)
☒ In arrears

505(b)(2)
(NDAs/NDA Efficacy Supplements only)

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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<tbody>
<tr>
<td></td>
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</tbody>
</table>

Is the application for a duplicate of a listed drug and eligible for approval under section 505(i) as an ANDA?

Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].

Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product’s active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?

If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs.

Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?

Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If yes, please list below:

<table>
<thead>
<tr>
<th>Application No.</th>
<th>Drug Name</th>
<th>Exclusivity Code</th>
<th>Exclusivity Expiration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

If there is unexpired, 3-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Designations and Approvals list at:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>-----------------------------------</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? <em>(NDAs/NDA efficacy supplements only)</em></td>
</tr>
<tr>
<td>[ ] Yes [ ] No [ ]</td>
</tr>
<tr>
<td>If yes, # years requested: 5 years</td>
</tr>
<tr>
<td>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use <em>(NDAs only)</em>?</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If yes, contact the Orange Book Staff <em>(CDER-Orange Book Staff)</em>.</th>
</tr>
</thead>
<tbody>
<tr>
<td>For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?</td>
</tr>
<tr>
<td>[ ] Yes [ ] No [ ]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</td>
</tr>
</tbody>
</table>

**Format and Content**

<table>
<thead>
<tr>
<th>Do not check mixed submission if the only electronic component is the content of labeling (COL).</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] All paper (except for COL) [ ] All electronic [ ] Mixed (paper/electronic)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] CTD [ ] Non-CTD [ ] Mixed (CTD/non-CTD)</td>
</tr>
<tr>
<td>Overall Format/Content</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>If electronic submission, does it follow the eCTD guidance?</td>
</tr>
<tr>
<td>If not, explain (e.g., waiver granted).</td>
</tr>
<tr>
<td>Index: Does the submission contain an accurate comprehensive index?</td>
</tr>
<tr>
<td>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>legible</td>
</tr>
<tr>
<td>English (or translated into English)</td>
</tr>
<tr>
<td>pagination</td>
</tr>
<tr>
<td>navigable hyperlinks (electronic submissions only)</td>
</tr>
<tr>
<td>If no, explain.</td>
</tr>
<tr>
<td>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</td>
</tr>
<tr>
<td>If yes, BLA #</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Forms and Certifications**

*Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, *paper* forms and certifications with hand-written signatures must be included.***

*Forms* include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); *Certifications* include: debarment certification, patent certification(s), field copy certification, and pediatric certification.

<table>
<thead>
<tr>
<th>Application Form</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are all establishments and their registration numbers listed on the form/attached to the form?</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patent Information (NDAs/NDA efficacy supplements only)</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Financial Disclosure</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are financial disclosure forms FDA 3454 and/or 3455</td>
<td>☐</td>
<td>☒</td>
<td>☐</td>
<td>Forms submitted but</td>
</tr>
</tbody>
</table>

---


Version: 4/15/2014 5

Reference ID: 3604946
included with authorized signature per 21 CFR 54.4(a)(1) and (3)?

**Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].**

*Note:* Financial disclosure is required for bioequivalence studies that are the basis for approval.

<table>
<thead>
<tr>
<th>Clinical Trials Database</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is form FDA 3674 included with authorized signature?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Debarment Certification</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is a correctly worded Debarment Certification included with authorized signature?</td>
<td></td>
<td></td>
<td></td>
<td>Correct wording &amp; signed by both Applicant and US Agent</td>
</tr>
<tr>
<td>*Certification is not required for supplements if submitted in the original application; <em>If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Note:</em> Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Field Copy Certification (NDAs/NDA efficacy supplements only)</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Controlled Substance/Product with Abuse Potential</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>If yes, date consult sent to the Controlled Substance Staff: CSS consult form will be entered into DARRTS once application is filed—CSS review team invited to Filing meeting</em></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>For non-NMEs:</th>
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</thead>
</table>
### Date of consult sent to Controlled Substance Staff:

<table>
<thead>
<tr>
<th>Pediatrics</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the application trigger PREA?</td>
<td></td>
<td></td>
<td></td>
<td>Full waiver requested—PMHS Sup. CSO invited to Filing Meeting</td>
</tr>
<tr>
<td>If yes, notify PeRC RPM (PeRC meeting is required)(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</td>
<td></td>
<td></td>
<td></td>
<td>Full waiver not granted until application--Agreed iPSP for full waiver under IND 63,901</td>
</tr>
<tr>
<td>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</td>
<td></td>
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</tr>
<tr>
<td>If no, request in 74-day letter</td>
<td></td>
<td></td>
<td></td>
<td>Studies impossible or highly impractical for Parkinson’s disease</td>
</tr>
<tr>
<td>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</td>
<td></td>
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</tr>
<tr>
<td>If no, request in 74-day letter</td>
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<tr>
<td>BPCA (NDAs/NDA efficacy supplements only):</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Is this submission a complete response to a pediatric Written Request?</td>
<td></td>
<td></td>
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<tr>
<td>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)(^3)</td>
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<tr>
<td>Proprietary Name</td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>Comment</td>
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<tr>
<td>Is a proposed proprietary name submitted?</td>
<td></td>
<td></td>
<td></td>
<td>Proprietary Name Denied under IND June 4, 2014. No additional request submitted to NDA</td>
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<tr>
<td>If yes, ensure that the application is also coded with the supporting document category, “Proprietary Name/Request for Review.”</td>
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<td>REMS</td>
<td>YES</td>
<td>NO</td>
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\(^2\) [http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff.ucm027829.htm](http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff.ucm027829.htm)

\(^3\) [http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff.ucm027837.htm](http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff.ucm027837.htm)
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<th>□</th>
<th>×</th>
<th>□</th>
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<tbody>
<tr>
<td><em>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</em></td>
<td>□</td>
<td>Not applicable</td>
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<tr>
<td><strong>Prescription Labeling</strong></td>
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<tr>
<td>Check all types of labeling submitted.</td>
<td>□</td>
<td>Package Insert (PI)</td>
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<tr>
<td></td>
<td></td>
<td>Patient Package Insert (PPI)</td>
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<tr>
<td></td>
<td></td>
<td>Instructions for Use (IFU)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Medication Guide (MedGuide)</td>
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<td></td>
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<td>Carton labels</td>
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<td></td>
<td></td>
<td>Immediate container labels</td>
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<tr>
<td></td>
<td></td>
<td>Diluent</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Other (specify)</td>
<td></td>
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<table>
<thead>
<tr>
<th>Is Electronic Content of Labeling (COL) submitted in SPL format?</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>If no, request applicant to submit SPL before the filing date.</em></td>
<td>□</td>
<td></td>
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<tr>
<td>Is the PI submitted in PLR format?</td>
<td>□</td>
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<tr>
<td><em>If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?</em></td>
<td>□</td>
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<td><em>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</em></td>
<td>□</td>
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<tr>
<td>All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?</td>
<td>□</td>
<td></td>
<td></td>
<td>Will enter consults upon filing—reviewers invited to filing meeting</td>
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<td>MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)</td>
<td>□</td>
<td></td>
<td></td>
<td>Will enter consults upon filing—reviewers invited to filing meeting</td>
</tr>
<tr>
<td>Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?</td>
<td>□</td>
<td></td>
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<td>Will enter consults upon filing—reviewers invited to filing meeting</td>
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<tr>
<td><strong>OTC Labeling</strong></td>
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<td>Outer carton label</td>
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<td>Immediate container label</td>
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<td>Blister card</td>
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<td>Blister backing label</td>
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<td>Consumer Information Leaflet (CIL)</td>
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<td>Physician sample</td>
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<td></td>
<td>Consumer sample</td>
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<td></td>
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<td>Other (specify)</td>
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<table>
<thead>
<tr>
<th>Is electronic content of labeling (COL) submitted?</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
</table>

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### If no, request in 74-day letter.

- Are annotated specifications submitted for all stock keeping units (SKUs)?
  - [ ] YES  [ ] NO  [ ] NA

### If no, request in 74-day letter.

- If representative labeling is submitted, are all represented SKUs defined?
  - [ ] YES  [ ] NO  [ ] NA

### If no, request in 74-day letter.

- All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?
  - [ ] YES  [ ] NO  [ ] NA

### Other Consults

- Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)
  - [x] YES  [ ] NO  [ ] NA
  - Comment: Nonclinical Biostat, QT-IRT, DTOP, DMPP

### If yes, specify consult(s) and date(s) sent:

#### Meeting Minutes/SPAs

- **End-of-Phase 2 meeting(s)?**
  - **Date(s):** November 8, 2005
  - [x] YES  [ ] NO  [ ] NA

- **Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?**
  - **Date(s):** August 29, 2013 (CMC), September 16, 2013
  - [x] YES  [ ] NO  [ ] NA

### If yes, distribute minutes before filing meeting

- **Any Special Protocol Assessments (SPAs)?**
  - **Date(s):** SPA 1&2 Exec CAC Communication October 6, 2005; SPA 3&4 No Agreement June 15, 2007; SPA 5 No Agreement October 10, 2008; SPA 6,7,8&9 SPA Request Denied November 4, 2009
  - [ ] YES  [ ] NO  [ ] NA

- **If yes, distribute letter and/or relevant minutes before filing meeting**
  - [ ] YES  [ ] NO  [ ] NA
  - SPA Requests:
    - SPA-1—carcinogenicity
    - SPA-2—carcinogenicity
    - SPA-3—Clinical
    - SPA-4—Clinical
    - SPA-5—Clinical
    - SPA-6—Clinical
    - SPA-7—Clinical
    - SPA-8—Clinical
    - SPA-9—Clinical
ATTACHMENT

MEMO OF FILING MEETING

DATE: July 10, 2014
NDA #: 207145

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: safinamide

DOSAGE FORM/STRENGTH: tablets, 50mg and 100mg

APPLICANT: Newron Pharmaceuticals, S.p.A.

PROPOSED INDICATION(S): • early stage patients being treated with a single dopamine agonist at a stable dose
• mid- to late stage patients receiving L-dopa and other Parkinson’s disease (PD) treatments

BACKGROUND: Safinamide is a new molecular entity proposed by Newron Pharmaceuticals for add-on treatment for Parkinson’s disease. The mechanism of action of the drug includes both dopaminergic (via inhibition of MAO-B) and non-dopaminergic (via inhibition of voltage-gated sodium channels) action. The IND under which US studies were conducted is 63,901. The Phase 3 program was initiated in 2004 and includes the following trials:

Add-on to a single dopamine agonist in early-stage PD
• One 12-week study
• Two 24-week placebo-controlled studies
• For patients completing the 24-week studies: the option of entry into a double-blind, placebo-controlled extension study and/or entry into an open-label study in which all patients received safinamide

Add-on to levodopa and other concomitant anti-Parkinson’s medications in mid- to late-stage PD patients
• Two 24-week placebo-controlled studies
• For patients completing the 24-week studies: the option of entry into a double-blind, placebo-controlled extension study and/or entry into an open-label study in which all patients received safinamide

The preNDA meeting to discuss the marketing application took place on September 16, 2013.
### REVIEW TEAM:

<table>
<thead>
<tr>
<th>Discipline/Organization</th>
<th>Names</th>
<th>Present at filing meeting? (Y or N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory Project Management</td>
<td>RPM: Stacy Metz, PharmD Tracy Peters, PharmD (covering application through November) Vandra Kishore, PharmD (covering meeting) CPMS/TL: Jacqueline Ware, PharmD</td>
<td>N N Y</td>
</tr>
<tr>
<td>Cross-Discipline Team Leader (CDTL)</td>
<td>G. David Podskalny, DO, MPHs</td>
<td>Y</td>
</tr>
<tr>
<td>Clinical</td>
<td>Reviewer: Leonard Kapcala, MD</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: G. David Podskalny, DO, MPHs</td>
<td>Y</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>Reviewer: Kristina Dimova, PhD</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Angela Men, PhD</td>
<td>Y</td>
</tr>
<tr>
<td>Biostatistics</td>
<td>Reviewer: Tristan Massie, PhD</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Kun Jin, PhD</td>
<td>Y</td>
</tr>
<tr>
<td>Nonclinical (Pharmacology/Toxicology)</td>
<td>Reviewer: LuAnn McKinney, PhD</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Lois Freed, PhD</td>
<td>Y</td>
</tr>
<tr>
<td>Statistics (carcinogenicity)</td>
<td>Reviewer: Atiar Mohammad Rahman, PhD</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>TL: Karl Lin, PhD</td>
<td>N</td>
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<tr>
<td>Product Quality (CMC) + CMC Labeling Review</td>
<td>Reviewer: Mohan Sapru, PhD Shastri Bhamidipati, PhD</td>
<td>N Y</td>
</tr>
<tr>
<td></td>
<td>TL: Martha Heimann, PhD</td>
<td>Y</td>
</tr>
<tr>
<td>Biopharmaceutics</td>
<td>Reviewer: Miverva Hughes, PhD</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Angelica Dorantes, PhD</td>
<td>Y</td>
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<tr>
<td>OSI/Clinical Inspection</td>
<td>Reviewer: Antoine El Hage, MD</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>TL: Susan Leibenhaut, MD</td>
<td>N</td>
</tr>
<tr>
<td>OSE/DMEPA</td>
<td>Reviewer: Danielle Naupauer, PharmD</td>
<td>Y</td>
</tr>
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<tr>
<td>TL:</td>
<td>Tingting Gao, PharmD</td>
<td>Y</td>
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<tr>
<td>Pharmacometrics</td>
<td>Reviewer: Hongshan Li, PhD</td>
<td>N</td>
</tr>
<tr>
<td>TL:</td>
<td>Anil Bhattacharya</td>
<td>Y</td>
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<tr>
<td>DRISK</td>
<td>Nyedra Booker, PharmD</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Jamie Wilkins Parker, PharmD</td>
<td>N</td>
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<td>DEPII</td>
<td>TL: Lockwood Taylor</td>
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<tr>
<td>Pediatrics</td>
<td>Rosemary Addy</td>
<td>N</td>
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<tr>
<td>DTOP</td>
<td>William Boyd, MD</td>
<td>N</td>
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<tr>
<td></td>
<td>Wiley Chambers, MD</td>
<td>N</td>
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<tr>
<td>CSS</td>
<td>Supervisor: Michael Klein, MD</td>
<td>N</td>
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<tr>
<td></td>
<td>PM: Sandra Saltz</td>
<td>N</td>
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<tr>
<td>Other DNP</td>
<td>Acting Director: Billy Dunn, MD</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Deputy Director: Eric Bastings, MD</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Deputy Director for Labeling: Nicole Bradley, PharmD</td>
<td>Y</td>
</tr>
<tr>
<td>Other attendees</td>
<td>Robert Temple, MD, ODE1, Acting Deputy Director (signatory authority)</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Tiffany Kong (Pharmacy Student)</td>
<td>Y</td>
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**FILING MEETING DISCUSSION:**

**GENERAL**

- 505(b)(2) filing issues:
  - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?
    - [ ] NO
    - [X] Not Applicable

  - Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?
    - [ ] NO
    - [ ] YES

  Describe the scientific bridge (e.g., BA/BE studies):

- Per reviewers, are all parts in English or English translation?
  - [ ] NO
  - [X] YES
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<tr>
<th><strong>If no</strong>, explain:</th>
<th></th>
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<tbody>
<tr>
<td>• Electronic Submission comments</td>
<td>□ Not Applicable</td>
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<tr>
<td><strong>List comments</strong>: Navigation issues</td>
<td></td>
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**CLINICAL**

**Comments**: Navigation issues affecting a large volume of material (>50,000 pages of tables in appendices); discrepancies between the location of ISS tables in the TOC, and the actual location in the appendix folders.

| • Clinical study site(s) inspections(s) needed? | □ YES |
| If no, explain: once filed | □ NO |

| • Advisory Committee Meeting needed? | □ YES |
| Comments: | Date if known: □ NO To be determined |

**If no, for an NME NDA or original BLA, include the reason. For example:**
- this drug/biologic is not the first in its class
- the clinical study design was acceptable
- the application did not raise significant safety or efficacy issues
- the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease

| • Abuse Liability/Potential | □ Not Applicable |
| Comments: | FILE |
| | □ REFUSE TO FILE |
| | □ Review issues for 74-day letter |

<p>| • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? | □ Not Applicable |
| Comments: | □ YES |
| | □ NO |</p>
<table>
<thead>
<tr>
<th>Section</th>
<th>Comments</th>
<th>ACTION</th>
<th>Review issues for 74-day letter</th>
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<tbody>
<tr>
<td>CLINICAL PHARMACOLOGY</td>
<td>Comments: not all studies submitted—comments for letter</td>
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<td>☑ Review issues for 74-day letter</td>
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<tr>
<td>The following Clinical Pharmacology information was not found in the NDA:</td>
<td>The Bioanalytical Report food-effect/absolute bioavailability trial.</td>
<td>☑ Yes</td>
<td>☑ Review issues for 74-day letter</td>
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<tr>
<td></td>
<td>The Bioanalytical Report for a study in patients with Renal impairment study,</td>
<td>☑ Yes</td>
<td>☑ Review issues for 74-day letter</td>
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<tr>
<td></td>
<td>The Pharmacokinetic (PK) results for 3 clinical trials.</td>
<td>☑ Yes</td>
<td>☑ Review issues for 74-day letter</td>
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<tr>
<td></td>
<td>The Sponsor’s analysis of a potential drug-drug interaction (safinamide with ropinirole).</td>
<td>☑ Yes</td>
<td>☑ Review issues for 74-day letter</td>
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<tr>
<td></td>
<td>Clinical pharmacology study site(s) inspections(s) needed?</td>
<td>☑ Yes</td>
<td>☑ Review issues for 74-day letter</td>
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<td>BIOSTATISTICS</td>
<td>Comments:</td>
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<td>☑ Review issues for 74-day letter</td>
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<td>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</td>
<td>Comments: None</td>
<td>☑ Not Applicable</td>
<td>☑ Review issues for 74-day letter</td>
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<td>PRODUCT QUALITY (CMC)</td>
<td>Comments:</td>
<td>☑ Not Applicable</td>
<td>☑ Review issues for 74-day letter</td>
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<tr>
<td>Environmental Assessment</td>
<td>Categorical exclusion for environmental assessment (EA) requested?</td>
<td>☑ Yes</td>
<td>☑ Review issues for 74-day letter</td>
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<td>If no, was a complete EA submitted?</td>
<td>☑ Yes</td>
<td>☑ Review issues for 74-day letter</td>
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<td>If EA submitted, consulted to EA officer (OPS)?</td>
<td>☑ Yes</td>
<td>☑ Review issues for 74-day letter</td>
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<tr>
<td>Comments:</td>
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<td>☑ No</td>
<td>☑ Review issues for 74-day letter</td>
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<td><strong>Facility Inspection</strong></td>
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<tr>
<td>• Establishment(s) ready for inspection?</td>
<td>☑ YES</td>
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<tr>
<td>■ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</td>
<td>☑ YES</td>
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**Comments:**

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**APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)**

<p>| | |</p>
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<tbody>
<tr>
<td>• 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 within 30 days after receipt of the original application?</td>
<td>☑ YES</td>
</tr>
<tr>
<td>From Pre-NDA Minutes: 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.</td>
<td></td>
</tr>
<tr>
<td>• If so, were the late submission components all submitted within 30 days?</td>
<td>☑ YES</td>
</tr>
<tr>
<td>• What late submission components, if any, arrived after 30 days?</td>
<td>N/A</td>
</tr>
<tr>
<td>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</td>
<td>☑ YES</td>
</tr>
<tr>
<td>Clinical Pharmacology-bioanalytical reports and pK study results. The Sponsor referenced a DMF that was submitted 3 weeks after the NDA. The DMF was not reviewable for another 3 weeks due to technical problems.</td>
<td></td>
</tr>
</tbody>
</table>
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?  
  □ NO  
  ☑ YES (2.7.6 SYNOPSIS OF INDIVIDUAL STUDIES with hyperlinks to site information)

• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?  
  □ NO  
  ☑ YES (356h establishment listing)

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Office level: Dr. Temple

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): to be determined

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:
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

REGULATORY CONCLUSIONS/DEFICIENCIES

☑ The application is unsuitable for filing. Explain why: Navigation issues

☐ The application, on its face, appears to be suitable for filing.

Review Issues:
  □ No review issues have been identified for the 74-day letter.
  □ Review issues have been identified for the 74-day letter. List (optional):

Review Classification:
  ☑ Standard Review

Version: 4/15/2014

Reference ID: 3604946
### ACTIONS ITEMS

- **Priority Review**

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑</td>
<td>Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug). --Done</td>
</tr>
<tr>
<td></td>
<td>If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).—N/A (consults not entered yet)</td>
</tr>
<tr>
<td></td>
<td>If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.</td>
</tr>
<tr>
<td></td>
<td>BLA/BLA supplements: If filed, send 60-day filing letter</td>
</tr>
</tbody>
</table>
| | If priority review:  
| | • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)  
| | • notify OMPQ (so facility inspections can be scheduled earlier) |
| | Send review issues/no review issues by day 74 |
| | Conduct a PLR format labeling review and include labeling issues in the 74-day letter—Noting in RTF letter that sponsor should do SRPI prior to resubmission |
| | Update the PDUFA V DARRTS page (for NME NDAs in the Program) |
| | BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f] |
|☑ | Notify sponsor by day 60 of filing decision |
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TRACY J PETERS
08/05/2014