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<td>PDUFA Goal Date</td>
<td>March 21, 2017</td>
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<td>OSE RCM #</td>
<td>2015-673</td>
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**Deputy Division Director**  
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**Review Completion Date**  
March 21, 2017

**Subject**  
Evaluation of Need for a REMS

**Established Name**  
Safinamide

**Trade Name**  
Xadago

**Name of Applicant**  
Newron Pharmaceuticals

**Therapeutic Class**  
Anti-Parkinson Drug; monoamine oxidase (MAO)-B inhibitor

**Formulation(s)**  
50 mg and 100 mg oral tablets

**Dosing Regimen**  
50 mg once daily, up to 100 mg once daily
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Xadago (safinamide) is necessary to ensure the benefits outweigh its risks. Newron Pharmaceuticals (Newron) resubmitted New Drug Application (NDA) 207145 for safinamide on September 21, 2016 after receipt of a Complete Response on March 28, 2016. The proposed indication is for adjunctive treatment to levodopa/carbidopa in patients with Parkinson’s Disease (PD) patients experiencing “off” episodes. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Neurology Products (DNP) agree that a REMS is not needed to ensure the benefits of safinamide outweigh its risks. Safinamide showed significant evidence of clinical efficacy for the adjunctive treatment to carbidopa/levodopa in patients with PD experiencing “off” episodes. There is adequate information presented in the proposed label to provide sufficient guidance to healthcare providers, patients, and the patient’s caregivers to ensure the safe use of safinamide.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Xadago (safinamide) is necessary to ensure the benefits outweigh its risks. Newron submitted a New Drug Application (NDA) 207145 safinamide on September 21, 2016 after receipt of a Complete Response on March 28, 2016. The proposed indication for adjunctive treatment to levodopa/carbidopa in patients with PD experiencing “off” episodes. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Safinamide, an alpha-aminoamide derivative, is a new molecular entity (NME). Safinamide is structurally unrelated to any other drug for the treatment of Parkinson’s disease, but is related to milacemide, an MAO-B inhibitor and glycine prodrug. Safinamide acts through multiple mechanisms of action. It inhibits voltage-gated sodium channels and, at higher concentrations, it inhibits calcium channels. The expected physiological effect is the modulation of the hyperactive neurons and the consequent regulation of neurotransmitter release, reducing the stimulated release of glutamate without affecting basal glutamate levels. Safinamide is also a reversible and selective MAO-B inhibitor whose selectivity for MAO-B is more than 1000-fold its selectivity for monoamine oxidase type A (MAO-A). Additionally, safinamide binds at the site of the dopamine transporter (DAT) and displaces the serotonin transporter (SERT) ligand, leading to uptake inhibition of dopamine and serotonin in the brain. Safinamide readily enters the brain, and has demonstrated both dopaminergic benefits

FDAAA factor (F): Whether the drug is a new molecular entity.
(increased levels of dopamine in the brain, extended efficacy of a given dose of levodopa on motor symptoms) and non-dopaminergic effects (reduced levodopa-induced dyskinesia) at plasma safinamide levels corresponding to therapeutic doses in clinical trials. In addition, safinamide has shown neuroprotective activity in preclinical models of PD as well as other central nervous system diseases, which is thought to result from non-dopaminergic mechanisms related to the partial inhibition of voltage-gated sodium channels and consequent normalization of excessive glutamate release. The terminal half-life is 20 to 26 hours, which allows once daily administration, and steady-state is reached within 5 to 6 days.\(^1\)

The Sponsor’s proposed indication for safinamide is for adjunctive treatment to levodopa/carbidopa in patients with PD experiencing “off” episodes. Safinamide will be formulated as 50mg and 100mg oral tablets, to be taken as a chronic therapy.\(^b\) The recommended starting dosage of safinamide is 50 mg administered orally once daily in the morning, without regard to meals. After taking 50 mg daily for two weeks, the dosage may be increased to 100 mg once daily, based on individual clinical need and tolerability. Patients with moderate hepatic impairment (Child-Pugh B: 7-9) should not exceed a maximum recommended dosage of 50 mg daily, and safinamide is contraindicated in patients with severe hepatic impairment (Child-Pugh C: 10-15). Patients taking safinamide who have a history of retinal/macular degeneration, uveitis, inherited retinal conditions, or progressive diabetic retinopathy should be periodically monitored for visual changes.

Safinamide was granted marketing authorization by the European Medicines Agency (EMA) on February 24, 2015, to be marketed in the European Union as an adjunct treatment for mid-to-late stage Parkinson’s disease, used with a dopamine (DA)-agonist or levodopa. The EMA authorization included the requirement for additional monitoring.

### 2.2 Regulatory History

The following is a summary of the regulatory history for NDA 207145 relevant to this review:

- **5/26/14:** The sponsor submitted safinamide for the adjunctive treatment to levodopa/carbidopa in patients with PD experiencing “off” episodes.
- **7/28/2014:** DNP issued a Refusal to File letter to the sponsor.
- **12/29/2014:** The sponsor resubmitted NDA 207145 after refusal to file from the Agency. The sponsor did not propose a REMS.
- **6/9/2015:** A Mid-Cycle meeting was held between the Agency and the sponsor via teleconference. The Agency informed the sponsor that, based on currently available data, a REMS was not needed for safinamide.

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\(^b\) FDAAA factor (D): The expected or actual duration of treatment with the drug.
• 3/28/2016: Complete Response (CR) letter sent to the sponsor due to deficiencies in characterizing abuse potential of safinamide, labeling deficiencies, and carton and container labeling.

• 7/21/2016: The sponsor and FDA met to ensure common understanding of issues in the CR letter and expected steps to be taken before the NDA can be approved.

• 9/21/2016: The sponsor resubmitted a complete, Class 2 response to the CR letter for NDA 207145.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition
Parkinson’s Disease (PD) is a chronic, progressive, neurodegenerative condition caused by the loss of dopamine-producing neurons in the nigrostriatal pathway of the brain, which leads to four classical primary symptoms: bradykinesia, tremor, muscle rigidity, and postural instability. Psychiatric manifestations, which include depression and visual hallucinations, are common, but not uniformly present, and dementia eventually occurs in at least 20% of cases. Parkinson’s disease begins between the ages of 45 and 70. An estimated 4% of PD patients are diagnosed before the age of 50, and the incidence increases with age; and is more common in men than women. PD affects an estimated one million people in the United States, and 7-10 million people worldwide, constituting about 1% of the population over the age of 65 years. c Parkinson’s disease affects more than the number of people diagnosed with multiple sclerosis, muscular dystrophy, and Lou Gehrig’s disease combined. PD leads to a deterioration in motor, mental, and functional skills and is associated with significantly raised mortality rates. It is chronic and associated with serious negative impacts on patients' social life, family, quality of life, work, and health. d

3.2 Description of Current Treatment Options
“The mainstay of the treatment for Parkinson’s disease is pharmacologic replacement of dopamine in the form of levodopa, which is converted to dopamine once it enters the brain. Levodopa, however, is associated with incapacitating motor fluctuations and dyskinesias. Other dopaminergic treatments have been added to clinical practice to reduce or delay the need for levodopa therapy, improve the efficacy of levodopa, or moderate its adverse effects. Other effective agents include dopamine agonists, inhibitors of catechol-O-methyltransferase (COMT) and monoamine oxidase-B (MAO-B), anticholinergics, and amantadine. As the disease progresses, patients may notice fluctuations between “on” periods, when they experience a good response to medication, and “off” periods, when the benefit from medications wears off and symptoms re-emerge. Treatment of advanced or disabling symptoms includes

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c FDAAA factor (A): The estimated size of the population likely to use the drug involved.

d FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.
neurosurgical procedures, such as deep brain stimulation of the subthalamic nucleus or globus pallidus. Occupational, physical, and speech therapy are often helpful.\textsuperscript{4}

In the early stages of PD, it is recommended that younger subjects delay the initiation of levodopa therapy, and, instead, start treatment with a dopamine agonist or MAO-B inhibitor. Inhibition of monoamine oxidase type B (MAO-B), the major enzyme metabolizing dopamine in the human brain, may help conserve the depleted supply of dopamine at synaptic levels, and delay the need for exogenous levodopa.\textsuperscript{5} However, as their disease progresses, the majority of subjects will require combination treatment to optimize their dopaminergic therapy. In patients with advanced PD who experience levodopa response fluctuations, MAO-B inhibition may potentiate and prolong its effects and permit a lower levodopa dose. Increasingly, non-dopaminergic agents are being studied to determine their potential to supplement or delay the use of established dopaminergic therapies. The following table is a summary of approved U.S. drugs for treating PD.

<table>
<thead>
<tr>
<th>Drugs approved in the U.S. for Treating Parkinson’s Disease</th>
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<tr>
<td>Early-Stage Indication</td>
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<tr>
<td>Ropinirole</td>
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<td>Pramipexole</td>
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<td>Rotigotine</td>
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<td>Rasagiline</td>
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<td>Apomorphine</td>
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<td>Entacapone</td>
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<td>Tolcapone</td>
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<td>Amantadine</td>
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4 Benefit Assessment

The Safinamide Phase II/III clinical development program was performed to support the claim that safinamide, at doses of 50 mg/day and 100 mg/day, is efficacious for the treatment of subjects with idiopathic Parkinson’s disease (PD) as add-on to:

- a single DA-agonist at a stable dose in early-stage subjects (ESPD); and
- levodopa alone or in combination with other PD medications in mid- to late-stage (LSPD) subjects
The program included one 12-week and two 24-week placebo-controlled studies evaluating safinamide as an add-on to a single DA-agonist in early-stage idiopathic PD patients (non-fluctuators), and two 24-week, placebo-controlled studies in mid- to late-stage idiopathic PD patients on levodopa and other concomitant anti-PD medications such as DA-agonists, catechol-o-methyltransferase (COMT) inhibitors, amantadine and anticholinergics (See Figure 1). Patients completing the 24-week trials could continue treatment in long-term (up to 18 months), double-blind, placebo-controlled extension studies, and/or enter an open-label study in which all patients received safinamide. An open-label study was conducted in a small group of Early PD patients treated with safinamide as add-on to anti-parkinsonian medications (DA-agonists or levodopa) for up to 24 months.

The PD Clinical Program also included two proof of concept (PoC) studies in PD patients, one (Study 701165-023) aimed at exploring the effect of safinamide in levodopa-induced dyskinesia (LID) and one (Study 701165-024) aimed at evaluating the effect of safinamide on cognition.

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**Figure 1. Safinamide Clinical Development Program (Source: Newron. Clinical Overview for Safinamide.)**

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### 4.1 Early Stage Parkinson’s Disease (ESPD)

The safety and efficacy of safinamide as add-on therapy to a single DA-agonist in ESPD patients not experiencing motor fluctuations (“non-fluctuators”) was demonstrated in three multi-center, double-blind, placebo-controlled pivotal trials: Study 9, Study 15, and Study MOTION. These studies had similar inclusion and exclusion criteria, and overall study design. The long-term efficacy and safety of safinamide in this patient population were assessed in Study 17, a one-year extension of Study 15. The pivotal studies for ESPD are described below, highlighting minor differences in design.

- **Study 9**: A 12-week, double-blind, placebo-controlled, randomized, Phases 2 and 3, dose-finding study. A total of 172 patients were randomized in a 1:1:1 ratio to placebo or two fixed
doses (0.5 mg/kg/day and 1 mg/kg/day, median doses of approximately 40 mg and 80 mg, respectively) of safinamide as add-on therapy to Parkinson’s disease patients who were either de novo (currently untreated) or receiving a single DA agonist at a stable dose.

• Study 15: A 24-week, double-blind, placebo-controlled, randomized, Phase 3 study to evaluate the safety and efficacy of safinamide as add-on therapy to ESPD patients who were receiving a single DA agonist at a stable dose. A total of 269 patients were randomized in a 1:1:1 ratio to safinamide 100 mg/day, safinamide 200 mg/day, or placebo.

• Study 17: A double-blind extension trial up to 48 weeks (or nearly one additional year of treatment) for patients who participated in Study 15. The primary efficacy endpoint was time to intervention.

• Study MOTION (Study 27938): A 24-week, double-blind, placebo-controlled, randomized, parallel-group, Phase 3, study to evaluate the safety and efficacy of safinamide as add-on therapy to early Parkinson’s disease patients who were receiving a single DA agonist at a stable dose. A total of 679 patients were randomized 1:1:1 to safinamide 50 mg/day, safinamide 100 mg/day, or placebo.

The primary efficacy endpoint for ESPD in the Phase 3 pivotal trials was the change from baseline in Part III of the unified Parkinson’s disease rating scale (UPDRS III) (motor subscale). The primary efficacy endpoint for ESPD the Sponsor used in the Phase 2 pivotal trial (Study 9) was the responder rate for a 30% or greater improvement (reduction from baseline) in UPDRS Part III. This, however, was not an acceptable primary efficacy endpoint for ESPD, according to the Division of Neurology Products (DNP). The DNP had informed the Sponsor that their primary interest for demonstrating efficacy in Study 9 would be the results of the change from baseline in UPDRS III, the Sponsor’s secondary endpoint in this trial. Other key secondary efficacy endpoints evaluated by the DNP included the change from baseline in UPDRS II (activities of daily living subscale) and other combinations of subscales.

4.2 Late/Advanced Stage Parkinson’s Disease (LSPD)
The safety and efficacy of safinamide in late stage Parkinson’s disease (LSPD) was evaluated in three Phase 3 pivotal studies.

• Study 16: A 24-week, double-blind, placebo-controlled, Phase 3, multi-center study. A total of 669 patients were randomized to safinamide doses of 50 mg/day and 100 mg/day as add-on therapy to a stable dose of levodopa in LSPD patients with motor fluctuations.

• Study 18: A double-blind extension trial (up to 1.5 years of additional treatment) for patients who participated in Study 16.

• Study SETTLE (Study 27919): A 24-week double-blind, placebo-controlled, parallel-group, Phase 3, multi-center study to evaluate the safety and efficacy of safinamide as add-on therapy to a stable dose of levodopa in LSPD patients with motor fluctuations. A total of 549 patients were randomized to safinamide 50 mg/day, 100 mg/day, or placebo.
Studies 16 and SETTLE for LSPD had similar inclusion criteria, exclusion criteria, and overall study design. The treatment difference (safinamide – placebo) for the primary efficacy endpoint (the change from baseline “on” time without troublesome dyskinesia) ranged from 0.5-1 hour for both safinamide doses in Study 16, and 1 hour in Study SETTLE. The treatment difference for decreasing “off” time (an important secondary endpoint) in each trial was similar to the respective magnitude of treatment difference for increasing “on” time without troublesome dyskinesia. According to the clinical reviewer, the therapeutic benefit demonstrated by safinamide was somewhat less than that of Zelapar (selegiline) and similar to Azilect (rasagiline) (0.8 - 1 hour), both recently approved MAO-B inhibitors.

Based upon the results of the safinamide clinical trial program, the Division of Neurology Products (DNP) has concluded that evidence of efficacy of safinamide as adjunctive treatment to levodopa/carbidopa in patients with Parkinson’s Disease (PD) experiencing “off” episodes, has been established.\(^e\)

## 5 Risk Assessment & Safe-Use Conditions

The safety population in the initial December 2014 submission of this NDA consisted of 1949 subjects with Parkinson’s disease who received at least one dose of safinamide in Phase 2 and Phase 3 placebo-controlled clinical studies or in the open-label studies. The review of safety focused primarily on the 1264 subjects who received safinamide at the proposed commercial dose of 50 mg/day to 100 mg/day. For the analyses of treatment emergent adverse events (TEAE), the safety population was categorized into three groupings by the Division of Neurology Products (DNP): early stage Parkinson’s disease (ESPD) (Study 15 and MOTION), late stage Parkinson’s disease (LSPD) (Study 16 and SETTLE), and the open-label extension studies.

The overall incidence of patients experiencing TEAE in the safinamide (76.1%) and placebo (75.8%) groups was similar. However, AEs in the system organ class (SOC) of CNS disorders were reported in at least 3% more patients taking safinamide than those taking placebo; however, this was only apparent in the ESPD group.

For the patients with ESPD, TEAEs were reported in a total of 375 (69.1%) of pooled safinamide (50 mg/day and 100 mg/day) patients (n=543), and in 221 (70.2%) of placebo patients (n=315). The incidence of the most frequently reported (>5%) adverse events in the safinamide vs. placebo groups were: dizziness (7 vs. 5.7%) and somnolence (5.7 vs. 7.3%), and were generally similar in safinamide and placebo groups.

With the resubmission of this application, the sponsor included a Safety Update which is limited to presentation and analysis of human safety data collected subsequent to the original December 2014 NDA submission. This safety update included results tabulated from 245 additional study subjects across two Phase 1 trials (ME2125-1, ME2125-2), a Phase 2/3 trial (ME2125-3), and one Phase 3 trial (ME2125-4) all conducted in Japan, in addition to post-marketing events from Europe, where safinamide

\(^e\) FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.
was approved on February 24, 2015. The serious adverse reactions (SARs) reported from the clinical trials and the Safety Update are detailed below.

5.1 Serious Adverse Events (SAEs)

In pooled studies for ESPD (Studies 15 and MOTION), the overall incidence of patients with at least one SAE was increased for patients treated with safinamide 50 mg (4%) and safinamide 100 mg (4%), compared to placebo (2%). There were no specific SAEs occurring in two or more patients. In the combined analysis of Study 15 with its extension phase (Study 17), the only specific SAE occurring in 2 (or more) patients was coronary artery disease, which was reported in 2% of patients taking safinamide 100 mg and 0% of patients taking safinamide 200 mg.

In the combined analysis of the LSPD Study 16 and its extension phase, Study 18, in which patients could have been treated for up to 2 years, the incidence of any SAE was 19% for all safinamide doses, 17% for safinamide 100 mg, 14% for safinamide 50 mg, and 14% for placebo. For most of the specific SAEs reported (femur fracture, myocardial infarction, cardiac failure, pneumonitis, renal failure, anemia, cataract) the difference in incidence between any safinamide group and placebo was only 1%.

Across all placebo-controlled studies, the incidence of patients discontinuing treatment was 5% for safinamide 50 mg, 6% for safinamide 100 mg, and 4% for placebo. The most frequently reported AE causing study discontinuation was dyskinesia.

No SAEs were reported in ME2125-1. Three SAEs occurred in the ongoing ME2125-3 study - all related to falls - with one patient experiencing a cervical vertebral fracture and another experiencing a rib fracture. In the ongoing ME2125-4 study, 7 SAEs occurred, including 1 death discussed below. The other six SAEs were:

- Upper respiratory infection with high fever leading to hospitalization
- Aggravated PD which subsequently led to hospitalization
- Intestinal obstruction
- Diagnosis of prostate cancer
- Neuroleptic Malignant Syndrome and renal failure

Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
• Femur fracture due to a fall

In the subject with aggravated PD, it began subsequent to taking 50 mg daily for 24 days, followed by 8 days on the 100 mg strength. The worsening motor fluctuations were not controlled by the increased dose, and subsequently led to hospitalization and discontinuation of safinamide. A contribution of safinamide to these events is considered possible. No relationship of safinamide is suspected in the causation of the other serious adverse events.

5.2 DEATHS

There were 61 deaths in the safinamide clinical program, which was conducted over 10 years. This included two deaths that occurred more than 30 days after the last dose of safinamide. The incidence rate was 2.6% in the safinamide group, compared with 1.2% in the placebo group. The clinical reviewer pointed out that a large number of safinamide patients were treated for more than six years, while a much smaller number of patients received placebo, and for a duration of up to only two years. The reviewer concluded that the difference in mortality rates may be explained by the much longer duration of treatment with safinamide compared to placebo. The exposure-adjusted mortality rate in LSPD patients demonstrates that, whether assessed for all deaths (n=28), or for those that occurred within 30 days of the last dose, whether over a 2-year period or 6-month period, no difference could be detected between safinamide and placebo.

One additional death was reported in the safety update; a 77 year old male subject was found drowned on the beach while swimming alone. No causal relationship was determined between safinamide and the drowning.

5.3 ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

5.3.1 Retinal Pathology

Pathologic changes were observed in the retina of albino and pigmented rats administered safinamide in multiple toxicity studies and a two-year carcinogenicity study. In these chronic studies, the thinning/degeneration of the retina progressed to a stage where the outer layer disappeared, and changes to the pigment epithelium and partial loss of the inner layer were also present. In pooled data from Studies 15 and 17, including patients taking safinamide for up to 1.5 years, the incidence of retinal degeneration was 2%, 0%, and 0% in patients taking safinamide 200 mg, 100 mg, and placebo, respectively. In this same population, the incidence of retinal pigmentation and pigment epitheliopathy was 0%, 2%, and 0% in patients taking safinamide 200 mg, 100 mg, and placebo, respectively. In pooled data from Studies 16 and 18, an abnormal retinal function test was reported in 1%, 2%, and 0% of patients taking safinamide 50 mg, 100 mg, and placebo, respectively. This potential risk may be confounded by the fact that research suggests that PD is associated with degenerative changes of the retinal nerve fiber layer. Retinal pathology will be communicated in the safinamide labeling in the Warnings and Precautions. Patients taking safinamide who have a history of retinal/macular degeneration, uveitis, inherited retinal conditions, family history of hereditary retinal disease, albinism, retinitis pigmentosa, or any active retinopathy should be periodically monitored for visual changes.
5.3.2 Hypersensitivity

Based on a post marketing surveillance report from Germany, the clinical reviewer recommended the addition of hypersensitivity to the labeling. The report stated that twenty days after starting safinamide, a subject experienced SAEs of a swollen tongue with dyspnea, redness in mouth, gingival swelling, rash on the trunk, appetite disorder with decreased appetite and increased appetite for sweets, inner restlessness, redness of face, pruritus, hyperhidrosis, dry mouth, hoarseness and malaise. Safinamide was withdrawn 2-3 days later and the subject recovered within two days. The patient was rechallenged with safinamide within 2-3 weeks, and developed the same clinical presentation, minus the rash on trunk, appetite disorder, dry mouth, and hoarseness. This overall presentation was less pronounced than the first cycle, and the subject recovered within 2 days of safinamide discontinuation. The resolution of these events in both instances following safinamide discontinuation is consistent with a positive dechallenge “response.” The clinical reviewer characterizes this syndrome as a “hypersensitivity” reaction/syndrome, which while not serious enough to be characterized as anaphylaxis, does follow the timeline of angioedema from a drug and should be considered a contraindication. A history of hypersensitivity to safinamide has been added to the safinamide labeling as a contraindication to therapy.

6 Expected Postmarket Use

Safinamide was approved in Europe in February 2015 and in Switzerland in November 2015. It has been marketed in Germany since May 2015, and other European countries (Belgium, Italy, Spain, Denmark, Netherlands, Sweden, United Kingdom, and Switzerland) have subsequently approved it, as well. Systematic data on the number of prescriptions dispensed is currently unavailable, however based on factory sales data, the approximate number of patients treated can be calculated. The total number of milligrams sold was determined, and the total number of patient years of exposure was calculated during the period of 24 February 2015 through 31 July 2016, assuming that patients were treated chronically. This calculation estimates approximately 10,490 patient-years of exposure, indicating a minimum of 10,490 patients have received treatment with at least one dose of safinamide. Thirty-six spontaneously reported post-marketing SAE’s were reported to the sponsor in this time, including the “hypersensitivity” reaction which is discussed in this review. Dr. Kapcala, the clinical reviewer, states that in addition to the Japanese studies, the European post-marketing data does not “change my impression of the safety profile for safinamide nor affect our ability to approve safinamide as a safe and effective drug and my recommendation is to approve safinamide.”

If it is approved in the United States, safinamide is likely to be prescribed by neurologists and movement disorder specialists. It is expected that the drug will be used in both an in-patient and out-patient setting. Patients with ESPD are likely to self-medicate, taking the tablets by mouth as directed by their healthcare provider. In LSPD, those who cannot self-medicate are likely to necessitate dispensation and/or administration of safinamide under the supervision of a caregiver. Adequate labeling that details the contraindications and warnings and precautions is necessary to communicate the risks of safinamide use to stakeholders.
7  Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for safinamide beyond routine pharmacovigilance and labeling. The Sponsor proposes that use of the label (physician’s Package Insert and the Patient Counseling Information) and compliance with standard safety reporting and pharmacovigilance requirements will suffice to mitigate risks and preserve benefits.

8  Discussion of Need for a REMS

Parkinson’s disease is a progressive neurodegenerative disease that affects an estimated 1 million people in the United States, and 7-10 million people worldwide, constituting about 1% of the population over the age of 65 years. PD leads to a deterioration in motor, mental, and functional skills and is associated with significantly raised mortality rates. It is chronic and associated with serious negative impacts on patients’ social life, family, quality of life, work, and health. The mainstay of treatment is pharmacologic replacement of dopamine in the form of levodopa. However, not only do the therapeutic effects of levodopa start to wear off, it is also associated with incapacitating motor fluctuations and dyskinesias. As the disease progresses, the majority of PD patients will require combination treatment to optimize their dopaminergic therapy. In patients taking levodopa who experience response fluctuations, MAO-B inhibition may potentiate and prolong the effects of dopamine and permit a lower levodopa dose. There is an increasing demand for new agents to supplement or delay the use of established dopaminergic therapies.

Based on results of two Phase 3 pivotal studies (Studies 16 and SETTLE) safinamide doses of 50 mg and 100 mg daily demonstrated safety and efficacy for increasing “on” time without troublesome dyskinesia and decreasing “off” time in patients with late stage Parkinson’s disease. The magnitude of safinamide’s therapeutic effect is similar to rasagiline, another recently approved MAO-B inhibitor.

The safety profile of safinamide is similar to other MAO-B inhibitors used to treat Parkinson’s disease. The most significant safety signal in the LSPD population was dyskinesia, an adverse event common to this class of medications. In addition, safety concerns associated with safinamide will be communicated through the prescribing information. Patients taking safinamide who have a history of retinal/macular degeneration, uveitis, inherited retinal conditions, or progressive diabetic retinopathy should be periodically monitored for visual changes.

The clinical review team has determined that the reported hypersensitivity reactions from post-marketing use in Europe demonstrates the need for additional labeling informing the risk of angioedema. Hypersensitivity to safinamide is included in the label as a contraindication to safinamide therapy, and similar post-marketing cases in the future should be monitored to further characterize this risk.

Newron, the clinical reviewer, stated that “the favorable risk/benefit profile and the lack of requirement for any specific medical monitoring indicates that a Risk Evaluation and Mitigation
Strategy (REMS) should not be required as an additional activity in managing the post-approval safe use of safinamide”. DRISK agrees that the adverse event profile of the drug does not warrant risk mitigation beyond labeling. Based on the currently available data, DRISK and DNP concur that a REMS is not necessary to ensure the benefits of safinamide outweigh the risks.

9 Conclusion & Recommendations

At this time, risk mitigation measures beyond professional labeling are not warranted for safinamide. Based on the currently available data, DRISK and DNP concur that the benefit-risk profile for safinamide is acceptable for the adjunctive treatment in Parkinson’s disease patients experiencing “off” episodes. Therefore, a REMS is not necessary to ensure the benefits outweigh the risks for safinamide.

10 Materials Reviewed

The following is a list of materials informing this review:


11 Appendices

11.1 REFERENCES

1 Kapcala L. Division of Neurology Products, Clinical Review of Safinamide, NDA 207145, March 29, 2016.


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/s/

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03/21/2017

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03/21/2017
Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: March 9, 2016
Reviewer: Erin Hachey, Pharm.D, Division of Risk Management (DRISK)
Acting Team Leader: Jamie Wilkins Parker, Pharm.D, DRISK
Division Director: Cynthia LaCivita, Pharm.D, DRISK

Subject: Evaluation to determine if a REMS is necessary
Drug Name(s): Xadago (safinamide)
Therapeutic Class: Anti-Parkinson drug; monoamine oxidase (MAO)-B inhibitor
Dosage and Route: 50 mg and 100 mg oral tablets
Proposed Indication: Treatment of signs and symptoms of early and advanced Parkinson’s disease
Application Type/Number: NDA 207145
Sponsor: Newron Pharmaceuticals
OSE RCM #: 2015-673

*** This document contains proprietary and confidential information that should not be released to the public. ***
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1 INTRODUCTION

This review by the Division of Risk Management’s (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Xadago (safinamide) oral tablets is necessary to ensure the benefits of this product outweigh its risks. A new drug application (NDA 207145) for safinamide was received on December 29, 2014, from Newron Pharmaceuticals, SpA (Newron), as a resubmission post-refusal to file (RTF). The proposed indication for safinamide is for adjunctive treatment in Parkinson’s disease (PD) patients experiencing “off” episodes while receiving levodopa, (b) (4). The intended patient population is patients with (b) (4) PD. The Sponsor did not include a proposed REMS or risk management plan for safinamide in this submission.

1.1 BACKGROUND OF CONDITION

Parkinson’s disease (PD) is a chronic, progressive, neurodegenerative condition caused by the loss of dopamine-producing neurons in the nigrostriatal pathway of the brain, which leads to four classical primary symptoms: bradykinesia, tremor, muscle rigidity, and postural instability. Psychiatric manifestations, which include depression and visual hallucinations, are common, but not uniformly present, and dementia eventually occurs in at least 20% of cases. Parkinson’s disease begins between the ages of 45 and 70. An estimated 4% of PD patients are diagnosed before the age of 50, and the incidence increases with age; and is more common in men than women. PD affects an estimated one million people in the United States, and 7-10 million people worldwide, constituting about 1% of the population over the age of 65 years. Parkinson’s disease affects more than the number of people diagnosed with multiple sclerosis, muscular dystrophy, and Lou Gehrig’s disease combined. PD leads to a deterioration in motor, mental, and functional skills and is associated with significantly raised mortality rates. It is chronic and associated with serious negative impacts on patients’ social life, family, quality of life, work, and health.4

“The mainstay of the treatment for Parkinson’s disease is pharmacologic replacement of dopamine in the form of levodopa, which is converted to dopamine once it enters the brain. Levodopa, however, is associated with incapacitating motor fluctuations and dyskinesias. Other dopaminergic treatments have been added to clinical practice to reduce or delay the need for levodopa therapy, improve the efficacy of levodopa, or moderate its adverse effects. Other effective agents include dopamine agonists, inhibitors of catechol-O-methyltransferase (COMT) and monoamine oxidase-B (MAO-B), anticholinergics, and amantadine. As the disease progresses, patients may notice fluctuations between “on” periods, when they experience a good response to medication, and “off” periods, when the benefit from medications wears off and symptoms re-emerge.5 Treatment of advanced or disabling symptoms includes neurosurgical


procedures, such as deep brain stimulation of the subthalamic nucleus or globus pallidus. Occupational, physical, and speech therapy are often helpful.\(^6\)

In the early stages of PD, it is recommended that younger subjects delay the initiation of levodopa therapy, and, instead, start treatment with a dopamine agonist or MAO-B inhibitor. Inhibition of monoamine oxidase type B (MAO-B), the major enzyme metabolizing dopamine in the human brain, may help conserve the depleted supply of dopamine at synaptic levels, and delay the need for exogenous levodopa.\(^7\) However, as their disease progresses, the majority of subjects will require combination treatment to optimize their dopaminergic therapy. In patients with advanced PD who experience levodopa response fluctuations, MAO-B inhibition may potentiate and prolong its effects and permit a lower levodopa dose. Increasingly, non-dopaminergic agents are being studied to determine their potential to supplement or delay the use of established dopaminergic therapies.\(^8\) The following table is a summary of approved U.S. drugs for treating PD.

<table>
<thead>
<tr>
<th>Drugs approved in the U.S. for Treating Parkinson's Disease</th>
<th>Early-Stage Indication</th>
<th>Late-Stage Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ropinirole</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Rasagiline</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Carbidopa/Levodopa</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Selegiline</td>
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<td>X</td>
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<tr>
<td>Apomorphine</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Entacapone</td>
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</tr>
<tr>
<td>Tolcapone</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Amantadine</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>


1.2 **PRODUCT BACKGROUND**

Safinamide, an alpha-aminoamide derivative, is a new molecular entity (NME). Safinamide is structurally unrelated to any other drug for the treatment of Parkinson’s disease, but is related to milacemide, an MAO-B inhibitor and glycine prodrug. Safinamide acts through multiple mechanisms of action. It inhibits voltage-gated sodium channels and, at higher concentrations, it inhibits calcium channels. The expected physiological effect is the modulation of the hyperactive neurons and the consequent regulation of neurotransmitter release, reducing the stimulated release of glutamate without affecting basal glutamate levels. Safinamide is also a reversible and selective MAO-B inhibitor whose selectivity for MAO-B is more than 1000-fold its selectivity for monoamine oxidase type A (MAO-A). Additionally, safinamide binds at the site of the dopamine transporter (DAT) and displaces the serotonin transporter (SERT) ligand, leading to uptake inhibition of dopamine and serotonin in the brain. Safinamide readily enters the brain, and has demonstrated both dopaminergic benefits (increased levels of dopamine in the brain, extended efficacy of a given dose of levodopa on motor symptoms) and non-dopaminergic effects (reduced levodopa-induced dyskinesia) at plasma safinamide levels corresponding to therapeutic doses in clinical trials. In addition, safinamide has shown neuroprotective activity in preclinical models of PD as well as other central nervous system diseases, which is thought to result from non-dopaminergic mechanisms related to the partial inhibition of voltage-gated sodium channels and consequent normalization of excessive glutamate release. The terminal half-life is 20 to 26 hours, which allows once daily administration, and steady-state is reached within 5 to 6 days.  

The Sponsor’s proposed indication for safinamide is for the treatment of patients with idiopathic Parkinson’s disease (PD), as add-on therapy to:

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

The recommended starting dosage of safinamide is 50 mg administered orally once daily in the morning, without regard to meals. After taking 50 mg daily for two weeks, the dosage may be increased to 100 mg once daily, based on individual clinical need and tolerability. Patients with moderate hepatic impairment (Child-Pugh B: 7-9) should not exceed a maximum recommended dosage of 50 mg daily, and safinamide is contraindicated in patients with severe hepatic impairment (Child-Pugh C: 10-15). Patients taking safinamide who have a history of retinal/macular degeneration, uveitis, inherited retinal conditions, or progressive diabetic retinopathy should be periodically monitored for visual changes.

Safinamide was granted marketing authorization by the European Medicines Agency (EMA) on February 24, 2015, to be marketed in the European Union as an adjunct treatment for mid-to-late

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9 Kapcala L. Division of Neurology Products, Draft Clinical Review of Safinamide, NDA 207145, viewed February 1, 2016.
stage Parkinson’s disease, used with a dopamine (DA)-agonist or levodopa. The EMA authorization included the requirement for additional monitoring.

1.3 Regulatory History

The following is a summary of the regulatory history for NDA 207145 relevant to this review:

**December 29, 2014:** The Agency received a resubmission after refusal to file from Newron for original NDA 207145 for safinamide for the adjunctive treatment of Parkinson’s disease patients experiencing “off” episodes while receiving concomitant levodopa. The Sponsor did not submit a proposed REMS.

**June 9, 2015:** A Mid-Cycle meeting was held between the Agency and the Sponsor via teleconference. The Agency informed the Sponsor that, based on the currently available data, a REMS was not needed for safinamide.

2 MATERIALS REVIEWED

The following is a list of materials that informed our review:

- Kapcala L. Division of Neurology Products, Draft Clinical Review of Safinamide, NDA 207145, viewed February 1, 2016.

3 RESULTS OF REVIEW

3.1 Overview of Clinical Program

The Safinamide Phase II/III clinical development program was performed to support the claim that safinamide, at doses of 50 mg/day and 100 mg/day, is efficacious for the treatment of subjects with idiopathic Parkinson’s disease (PD) as add-on to:

- a single DA-agonist at a stable dose in early-stage subjects (ESPD); and
- levodopa alone or in combination with other PD medications in mid- to late-stage (LSPD)

The program included one 12-week and two 24-week placebo-controlled studies evaluating safinamide as an add-on to a single DA-agonist in early-stage idiopathic PD patients (non-fluctuators), and two 24-week, placebo-controlled studies in mid- to late-stage idiopathic PD patients on levodopa and other concomitant anti-PD medications such as DA-agonists, catechol-o-methyltransferase (COMT) inhibitors, amantadine and anticholinergics (See Figure 1). Patients completing the 24-week trials could continue treatment in long-term (up to 18 months), double-blind, placebo-controlled extension studies, and/or enter an open-label study in which all patients received safinamide. An open-label study was conducted in a small group of Early PD patients...
treated with safinamide as add-on to anti-parkinsonian medications (DA-agonists or levodopa) for up to 24 months.

The PD Clinical Program also included two proof of concept (PoC) studies in PD patients, one (Study 701165-023) aimed at exploring the effect of safinamide in levodopa-induced dyskinesia (LID) and one (Study 701165-024) aimed at evaluating the effect of safinamide on cognition.

3.1.1 Early Stage Parkinson’s Disease (ESPD)

The safety and efficacy of safinamide as add-on therapy to a single DA-agonist in ESPD patients not experiencing motor fluctuations (“non-fluctuators”) was demonstrated in three multi-center, double-blind, placebo-controlled pivotal trials: Study 9, Study 15, and Study MOTION. These studies had similar inclusion and exclusion criteria, and overall study design. The long-term efficacy and safety of safinamide in this patient population were assessed in Study 17, a one-year extension of Study 15. The pivotal studies for ESPD are described below, highlighting minor differences in design.

- **Study 9:** A 12-week, double-blind, placebo-controlled, randomized, Phases 2 and 3, dose-finding study. A total of 172 patients were randomized in a 1:1:1 ratio to placebo or two fixed doses (0.5 mg/kg/day and 1 mg/kg/day, median doses of approximately 40 mg and 80 mg, respectively) of safinamide as add-on therapy to Parkinson’s disease patients who were either de novo (currently untreated) or receiving a single DA agonist at a stable dose.
• **Study 15:** A 24-week, double-blind, placebo-controlled, randomized, Phase 3 study to evaluate the safety and efficacy of safinamide as add-on therapy to ESPD patients who were receiving a single DA agonist at a stable dose. A total of 269 patients were randomized in a 1:1:1 ratio to safinamide 100 mg/day, safinamide 200 mg/day, or placebo.

• **Study 17:** A double-blind extension trial up to 48 weeks (or nearly one additional year of treatment) for patients who participated in Study 15. The primary efficacy endpoint was time to intervention.

• **Study MOTION (Study 27938):** A 24-week, double-blind, placebo-controlled, randomized, parallel-group, Phase 3, study to evaluate the safety and efficacy of safinamide as add-on therapy to early Parkinson’s disease patients who were receiving a single DA agonist at a stable dose. A total of 679 patients were randomized 1:1:1 to safinamide 50 mg/day, safinamide 100 mg/day, or placebo.

The primary efficacy endpoint for ESPD in the Phase 3 pivotal trials was the change from baseline in Part III of the unified Parkinson’s disease rating scale (UPDRS III) (motor subscale). The primary efficacy endpoint for ESPD the Sponsor used in the Phase 2 pivotal trial (Study 9) was the responder rate for a 30% or greater improvement (reduction from baseline) in UPDRS Part III. This, however, was not an acceptable primary efficacy endpoint for ESPD, according to the Division of Neurology Products (DNP). The DNP had informed the Sponsor that their primary interest for demonstrating efficacy in Study 9 would be the results of the change from baseline in UPDRS III, the Sponsor’s secondary endpoint in this trial. Other key secondary efficacy endpoints evaluated by the DNP included the change from baseline in UPDRS II (activities of daily living subscale) and other combinations of subscales.

### 3.1.2 Late/Advanced Stage Parkinson’s Disease (LSPD)

The safety and efficacy of safinamide in late stage Parkinson’s disease (LSPD) was evaluated in three Phase 3 pivotal studies.

• **Study 16:** A 24-week, double-blind, placebo-controlled, Phase 3, multi-center study. A total of 669 patients were randomized to safinamide doses of 50 mg/day and 100 mg/day as add-on therapy to a stable dose of levodopa in LSPD patients with motor fluctuations.

• **Study 18:** A double-blind extension trial (up to 1.5 years of additional treatment) for patients who participated in Study 16.

• **Study SETTLE (Study 27919):** A 24-week double-blind, placebo-controlled, parallel-group, Phase 3, multi-center study to evaluate the safety and efficacy of safinamide as add-on therapy to a stable dose of levodopa in LSPD patients with motor fluctuations. A total of 549 patients were randomized to safinamide 50 mg/day, 100 mg/day, or placebo.

Studies 16 and SETTLE for LSPD had similar inclusion criteria, exclusion criteria, and overall study design. The treatment difference (safinamide – placebo) for the primary efficacy endpoint (the change from baseline “on” time without troublesome dyskinesia) ranged from 0.5-1 hour for both safinamide doses in Study 16, and 1 hour in Study SETTLE. The treatment difference for decreasing “off” time (an important secondary endpoint) in each trial, was similar to the respective magnitude of treatment difference for increasing “on” time without troublesome
dyskinesia. According to the clinical reviewer, the therapeutic benefit demonstrated by safinamide was somewhat less than that of Zelapar (selegiline) and similar to Azilect (rasagiline) (0.8 - 1 hour), both recently approved MAO-B inhibitors.

3.2 **SAFETY CONCERNS**

The total safety population consisted of 1949 subjects with Parkinson’s disease who received at least one dose of safinamide in Phase 2 and Phase 3 placebo-controlled clinical studies or in the open-label studies. The review of safety focused primarily on the 1264 subjects who received safinamide at the proposed commercial dose of 50 mg/day to 100 mg/day. For the analyses of treatment emergent adverse events (TEAE), the safety population was categorized into three groupings by the Division of Neurology Products (DNP): early stage Parkinson’s disease (ESPD) (Study 15 and MOTION), late stage Parkinson’s disease (LSPD) (Study 16 and SETTLE), and the open-label extension studies.

The overall incidence of patients experiencing TEAE in the safinamide (76.1%) and placebo (75.8%) groups was similar. However, AEs in the system organ class (SOC) of CNS disorders were reported in at least 3% more patients taking safinamide than those taking placebo; however, this was only apparent in the ESPD group.

For the patients with ESPD, TEAEs were reported in a total of 375 (69.1%) of pooled safinamide (50 mg/day and 100 mg/day) patients (n=543), and in 221 (70.2%) of placebo patients (n=315). The incidence of the most frequently reported (>5%) adverse events in the safinamide vs. placebo groups were: dizziness (7 vs. 5.7%) and somnolence (5.7 vs. 7.3%), and were generally similar in safinamide and placebo groups.

3.2.1 **Serious Adverse Events (SAEs)**

In pooled studies for ESPD (Studies 15 and MOTION), the overall incidence of patients with at least one SAE was increased for patients treated with safinamide 50 mg (4%) and safinamide 100 mg (4%), compared to placebo (2%). There were no specific SAEs occurring in two or more patients. In the combined analysis of Study 15 with its extension phase (Study 17), the only specific SAE occurring in 2 (or more) patients was coronary artery disease, which was reported in 2% of patients taking safinamide 100 mg and 0% of patients taking safinamide 200 mg.

In the combined analysis of the LSPD Study 16 and its extension phase, Study 18, in which patients could have been treated for up to 2 years, the incidence of any SAE was 19% for all safinamide doses, 17% for safinamide 100 mg, 14% for safinamide 50 mg, and 14% for placebo. For most of the specific SAEs reported (femur fracture, myocardial infarction, cardiac failure, pneumonitis, renal failure, anemia, cataract) the difference in incidence between any safinamide group and placebo was only 1%.

Across all placebo-controlled studies, the incidence of patients discontinuing treatment was 5% for safinamide 50 mg, 6% for safinamide 100 mg, and 4% for placebo The most frequently reported AE causing study discontinuation was dyskinesia.
3.2.2 Deaths

There were 61 deaths in the safinamide clinical program, which was conducted over 10 years. This included two deaths that occurred more than 30 days after the last dose of safinamide. The incidence rate was 2.6% in the safinamide group, compared with 1.2% in the placebo group. The clinical reviewer pointed out that a large number of safinamide patients were treated for more than six years, while a much smaller number of patients received placebo, and for a duration of up to only two years. The reviewer concluded that the difference in mortality rates may be explained by the much longer duration of treatment with safinamide compared to placebo. The exposure-adjusted mortality rate in LSPD patients demonstrates that, whether assessed for all deaths (n=28), or for those that occurred within 30 days of the last dose, whether over a 2-year period or 6-month period, no difference could be detected between safinamide and placebo.

3.2.3 Adverse Events of Special Interest (AESI)

3.2.3.1 Retinal Pathology

Pathologic changes were observed in the retina of albino and pigmented rats administered safinamide in multiple toxicity studies and a two-year carcinogenicity study. In these chronic studies, the thinning/degeneration of the retina progressed to a stage where the outer layer disappeared, and changes to the pigment epithelium and partial loss of the inner layer were also present. In pooled data from Studies 15 and 17, including patients taking safinamide for up to 1.5 years, the incidence of retinal degeneration was 2%, 0%, and 0% in patients taking safinamide 200 mg, 100 mg, and placebo, respectively. In this same population, the incidence of retinal pigmentation and pigment epitheliopathy was 0%, 2%, and 0% in patients taking safinamide 200 mg, 100 mg, and placebo, respectively. In pooled data from Studies 16 and 18, an abnormal retinal function test was reported in 1%, 2%, and 0% of patients taking safinamide 50 mg, 100 mg, and placebo, respectively. This potential risk may be confounded by the fact that research suggests that PD is associated with degenerative changes of the retinal nerve fiber layer. Retinal pathology will be communicated in the safinamide labeling. However, discussions are currently ongoing to determine whether it will be included in the Contraindications or Warnings and Precautions section. Patients taking safinamide who have a history of retinal/macular degeneration, uveitis, inherited retinal conditions, or progressive diabetic retinopathy should be periodically monitored for visual changes.

4 DISCUSSION

Parkinson’s disease is a progressive neurodegenerative disease that affects an estimated 1 million people in the United States, and 7-10 million people worldwide, constituting about 1% of the population over the age of 65 years. PD leads to a deterioration in motor, mental, and functional skills and is associated with significantly raised mortality rates. It is chronic and associated with serious negative impacts on patients' social life, family, quality of life, work, and health. The mainstay of treatment is pharmacologic replacement of dopamine in the form of levodopa. However, not only do the therapeutic effects of levodopa start to wear off, it is also associated with incapacitating motor fluctuations and dyskinesias. As the disease progresses, the majority of PD patients will require combination treatment to optimize their dopaminergic therapy. In
patients taking levodopa who experience response fluctuations, MAO-B inhibition may potentiate and prolong the effects of dopamine and permit a lower levodopa dose. There is an increasing demand for new agents to supplement or delay the use of established dopaminergic therapies.

Based on results of two Phase 3 pivotal studies (Studies 16 and SETTLE) safinamide doses of 50 mg and 100 mg daily demonstrated safety and efficacy for increasing “on” time without troublesome dyskinesia and decreasing “off” time in patients with late stage Parkinson’s disease. The magnitude of safinamide’s therapeutic effect is similar to rasagiline, another recently approved MAO-B inhibitor.

The safety profile of safinamide is similar to other MAO-B inhibitors used to treat Parkinson’s disease. The most significant safety signal in the LSPD population was dyskinesia, an adverse event common to this class of medications. In addition, safety concerns associated with safinamide will be communicated through the prescribing information. Patients taking safinamide who have a history of retinal/macular degeneration, uveitis, inherited retinal conditions, or progressive diabetic retinopathy should be periodically monitored for visual changes.

Therefore, based on the currently available data, DRISK and DNP concurred that a REMS is not necessary to ensure the benefits of safinamide outweigh the risks.

5 CONCLUSION

At this time, risk mitigation measures beyond professional labeling are not warranted for safinamide. Based on the currently available data, DRISK and DNP concurred that the benefit-risk profile for safinamide is acceptable for the adjunctive treatment in Parkinson’s disease patients experiencing “off” episodes in addition to levodopa, with or without other dopaminergic medications. Therefore, a REMS is not necessary to ensure the benefits outweigh the risks for safinamide. If new safety information becomes available, please consult DRISK.
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