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APPLICATION NUMBER:

207145Orig1s000

OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Deputy Office Director Summary Review
NDA/BLA #	207,145
Applicant Name	Newron Pharmaceuticals S.p.A.
Date of Submission	Dec 29, 2014 (initial) Sept 21, 2016 (resubmission)
PDUFA Goal Date	March 21, 2017
Proprietary Name / Established (USAN) Name	Xadago /safinamide
Dosage Forms / Strength	Tablet 50 mg, 100 mg
Proposed Indication(s)	Add-on therapy to (b) (4) L-dopa alone or in combination with other PD drugs in mid to late-stage (b) (4) PD patients.
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Deputy Division Director Review	Eric Bastings
Regulatory Health Project Manager	Stacy Metz
Medical Officer Review	Leonard Kapcala
Statistical Review	Xiangmin Zhang
Pharmacology Toxicology Review	LuAnn McKinney
Clinical Pharmacology Review	Histrina Dimova
OPDP	Aline Moukhtara
OSI	Antoine El-Hage
CDTL Review	Gerald D. Podskalny
OSE/DMEPA	Justine Harris
OSE/DRISK	Erin Hachey
OPQ/Drug Substance	Sharon Kelly
OPQ/Drug Product	Sherita McLamore
OPQ/Process/Microbiology	Mark Johnson
OPQ/Facility	Tracie Sharp/Franck Wackes
OPQ/Biopharmaceutics	Okpo Eradiri
OPQ/Project/Business Process Manager	Dahlia A. Woody
OPQ/Application Technical Lead	Martha R. Heimann
OPQ/ Environmental Assessment	James Laurenson
Ophthalmology	Wiley Chambers
Controlled Substance Staff	Alicja Lerner/Jonita Randall-Thompson
QT Study Review	Huifang Chen

OND=Office of New Drugs
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 OSI=Office of Scientific Investigations
 DRISK=Division of Risk Management
 CDTL=Cross-Discipline Team Leader
 OPQ=Office of Pharmaceutical Quality

I. Introduction

NDA 207145 initially proposed the use of safinamide, a selective monoamine oxidase Type B (MAO-B) inhibitor as: 1) a treatment for add-on to a dopamine agonist in early Parkinson's Disease (PD) and 2) use with (b) (4) levodopa, alone or in combination with other PD drugs, in later stage disease (b) (4) (b) (4).

The initial submission on Dec 29, 2015 received a *Complete Response* (CR) on March 28, 2016 because of deficiencies in the controlled substance/abuse liability assessment of safinamide, deficiencies in both non-clinical assessment of abuse potential related to sedative effects and clinical evaluation of dependence and withdrawal effects of safinamide. The review also concluded that the early PD indication was not adequately supported.

The CR letter included an initial proposed labeling, which has since been discussed and modified.

This Deputy Office Director Decisional Memo includes most of the content of the March 28, 2016 CR memo, with modifications to account for new data on abuse potential and some additional safety data.

II. Background

Safinamide is a selective monoamine oxidase Type B (MAO-B) inhibitor, pharmacologically similar to selegiline and rasagiline. These drugs are used in patients with PD to improve movement. They block catabolism (breakdown) of dopamine, increasing dopamine levels and dopamine activity in the brain. There were two uses proposed by the applicant: 1) use as add-on to a single dopamine agonist (such as rotigotine, ropinirole, lisuride, pramipexole), in early stage PD, and 2) use in combination with (b) (4) levodopa, alone or in combination with other PD drugs, in mid-to-late-stage (b) (4) PD patients. For the latter proposed use the aim is to increase the total daily "ON" time, i.e., total "ON" time without dyskinesia plus "ON" time with non-troublesome dyskinesia over the 18-hour diary recording period, and to reduce total "OFF" time, periods in which PD patients revert to the immobility characteristic of the disease. In the early PD use, effects were measured using the Unified Parkinson's Disease Rating Scale (UPDRS), items II (Activities of Daily Living) and III (Motor Examination).

As described fully in reviews by Drs. Kapcala, Zhang, Podskalny, and Bastings, the 3 studies intended to support early use did not really do so, and all recommend that this claim not be approved. All, however, support the effectiveness of safinamide as add-on treatment for patients with mid- to late-stage PD on (b) (4) levodopa.

There are no product quality or clinical microbiology issues and these areas will not be discussed. PD is extremely rare in the pediatric population and pediatric studies are not feasible. A pediatric waiver will therefore be issued.

A metabolite of safinamide (NW-1689) inhibits BCRP (Breast Cancer Resistance Protein), which metabolizes many potentially toxic drugs (see Safety Section V below).

III. Clinical Pharmacology

As discussed by Dr. Bastings, safinamide is metabolized primarily by hepatic non-microsomal enzymes, cytosolic amidates (e.g., MAO-A) and only minimally by cytochrome P450 enzymes, with the multiple metabolic pathways leaving little potential for important drug-drug interactions. The > 95% metabolic transformation to non-active metabolites also obviates the need for adjustment for renal impairment.

IV. Clinical/Statistical

A. Early Disease – Use as an add-on to a dopamine agonist.

All reviewers (Kapcala, Podskalny, Zhang) and Dr. Bastings agree that the 3 studies do not provide substantial evidence of effectiveness, but there are clearly some “trends,” and Dr. Bastings has noted and assessed these. All 3 studies comparing safinamide to placebo in early PD used the Unified Parkinson’s Disease Rating Scale (UPDRS) III scale as the primary endpoint, comparing average score as the endpoint in 2 studies and the rates of 30% improvement in one study. In the studies safinamide was added to a single dopamine agonist (Studies 015 and 27918 and many patients in Study 009) or to no other therapy (some patients in Study 009). The studies were of 12 (Study 009) or 24 (Studies 015, 27918) weeks duration. All 3 studies compared 2 doses to placebo. Study 27918 evaluated the same 2 doses as the mid-to-late disease studies, 50 and 100 mg, and did not show statistically significant improvement compared to placebo on UPDRS Section III, although the p-value of 0.07 at the 100-mg dose was close to significant (p = 0.2 at the 50-mg dose). Study 015 studied doses of 100 mg and 200 mg, showing essentially no effect (p = 0.65) at the higher dose, blocking further statistical analysis (but the lower dose suggested effectiveness, with a nominal p = 0.04). Both studies thus provided a suggestion of an effect, but not convincing evidence. The first study, 009, used mg/kg dosing, averaging 39 and 78 mg/day, which would still be informative, had the study been successful, and its primary endpoint was the rate of 30% reduction (improvement) in UPDRS Part III, called a “response,” which allowed calculation of responder rates. The responder rate evaluation (not used previously in this condition) was statistically significant, with 21/56 on the higher dose vs 12/56 on placebo, i.e., 37.5% vs 21.4%, (p = 0.006) at the higher dose. The mean change in UPDRS score (the endpoint measure used in the other 2 studies), however, was not statistically significant; p = 0.19.

Dr. Bastings finds Study 009 at least somewhat supportive of effectiveness, but on the responder rate endpoint, not previously used and of at least debatable clinical meaning. As noted, analysis of UPDRS scores was not close to significant in Study 009 using the planned Kruskal-Wallis test, although a later ANCOVA analysis did give statistical significance. The fact that the two substantially larger studies, 015 and 27918, did not really confirm a suggested effect weakens the 009 finding, although, again, they were not wholly negative. The overall data led him to conclude that there was not sufficient evidence to support approval of safinamide in the early PD population, and I concur. The full data are considered in Dr. Bastings’ review, and they are summarized in Table 1 below, taken from various reviews.

Table I - Early Disease

Study	Low Dose	High Dose	Placebo
Study 009 (Podskalny, p 30)	n = 55 0.5 mg/kg	n = 56 1.0 mg/kg	n = 56
Baseline UPDRS III	16.4	16.5	17.3
Final Visit (mean)	13.8	13.2	16.7
Change from baseline	- 2.6	- 3.3	- 0.6
p-value		0.19	
Study 015 (Podskalny, p 32)	n = 86 100 mg/d	n = 81 200 mg/d	n = 87
Baseline UPDRS III	22.0	19.3	20.7
Final Visit (mean)	16.3	15.6	17.1
Change from baseline	- 6.0	- 3.9	- 3.6
p-value	0.04	0.65	
MOTION Study 27918 (Kapcala, p 56)	n = 227 50 mg/d	n = 227 100 mg/d	n = 225
Baseline UPDRS III	21.0	18.9	19.8
Week 24	19.0	16.9	18.0
Change from baseline	1.60	-1.98	-0.95
Change vs placebo	-0.65	-1.04	
p-value	0.259	0.073	

B. Late Disease – Mid-to-Late-State PD as Add-on to L-dopa

This claim is supported by 2 studies of substantial size, studies 016 and 27919 (SETTLE), with 669 and 549 patients, respectively. Both studies utilized a 10-day screening period to optimize background PD treatments to minimize motor symptoms, followed by a 4-week levodopa stabilization phase. Patients were then randomized to 50 or 100 mg of safinamide or placebo (Study 016), or to safinamide 100 mg or to placebo (SETTLE). In SETTLE patients were started on 50 mg, then titrated to 100 mg, as tolerated (dose could be reduced to 50 mg) and followed for 24 weeks. The primary endpoint was “ON” time without troublesome dyskinesia (referred to later in this memo as “ON” time) measured in an 18-hour diary, the Parkinson’s Disease Patient Diary. Secondary endpoints included total daily “OFF” time and UPDRS III. UPDRS II (activities of daily living) was also examined.

Results of the 2 studies are shown in Table 2 (Zhang review). There was a significant increase of about 0.5 (Study 016) to 1 (Study 27919) hour in “ON” time and a similar decrease in “OFF” time. The UPDRS III was also improved. There was no suggestion of a greater response of “ON” time with the higher dose but some indication of increased response of UPDRS III. The higher dose will be included as a possibility in labeling, with monitoring for tolerability.

Table 2

Study 016	Low Dose n = 217 50 mg	High Dose n = 216 100mg	Placebo n = 212
Baseline ON	9.41	9.66	9.29
Final ON	10.88	11.01	10.32
Change in ON	1.37	1.37	0.97
LS Difference from placebo	0.50	0.53	
p-value (MMRM analysis)	0.0356	0.0238	
LS Diff from placebo in OFF	-0.54	-0.53	
p-value (MMRM analysis)	0.0088	0.0110	
LS Difference from placebo in UPDRS III	-1.71	-2.24	
p-value (MMRM analysis)	0.0373	0.0065	

SETTLE Study 27919	Safinamide n = 268 100 mg	Placebo n = 273
Baseline ON	9.30	9.09
Final ON	10.72	9.63
Change in ON	1.44	0.53
LS Difference from placebo in ON	0.99	
p-value	< 0.001	
Change from Baseline in OFF	-1.58	-0.52
LS Difference from placebo OFF	-1.06	
p-value	<0.001	
UPDRS III		
Change from baseline	-3.50	-2.05
LS Difference from placebo	-1.70	
p-value	<0.005	

The time course of improvement in “ON” time was similar in both studies (figures 1, 2 from Dr. Zhang’s review). There was no suggestion of an earlier or larger response at the higher dose in Study 016.

Figure 1. Study 016 mean (\pm standard error) of change from Baseline in total daily "on" time by week and treatment

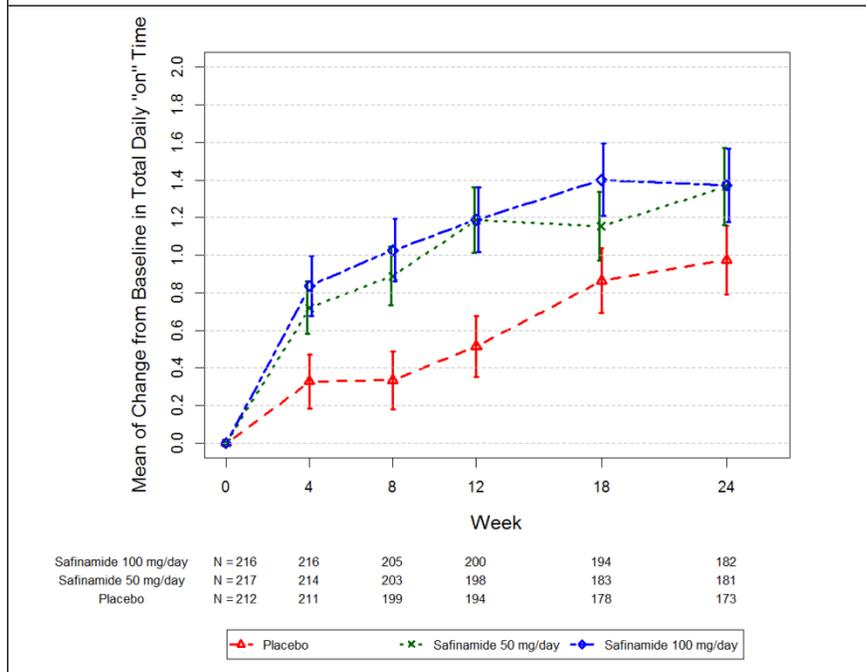
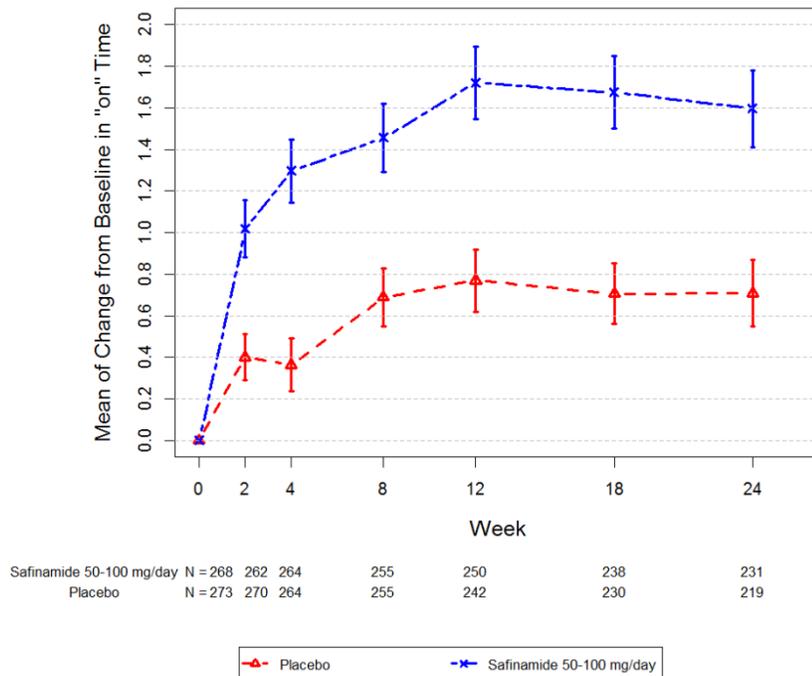


Figure 2. Study 27919 mean (\pm standard error) of change from Baseline in total daily "on" time by week and treatment



The cumulative distribution curves for Study 016 show the roughly half-hour difference between treatments (figure 3) with little sign of a subgroup with a larger response. The curve for Study 27919 shows the somewhat larger mean response in that study with perhaps a suggestion of some stronger responders.

Figure 3. Study 016 empirical cumulative distribution functions for the change from Baseline to Week 24 in total daily “on” time

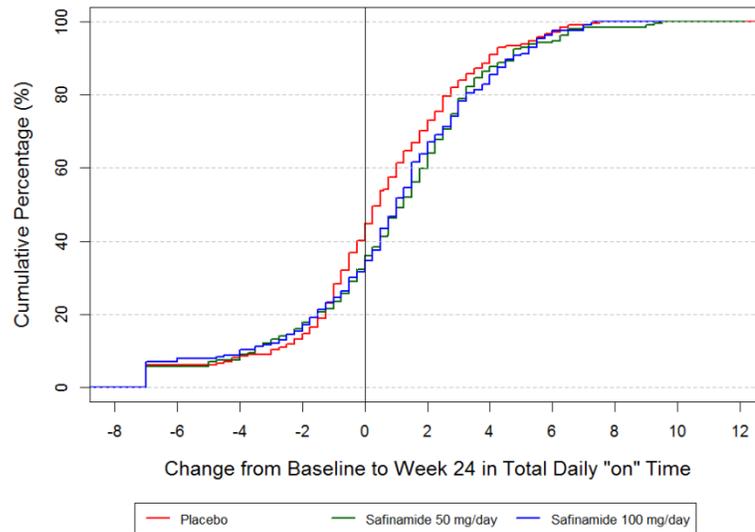
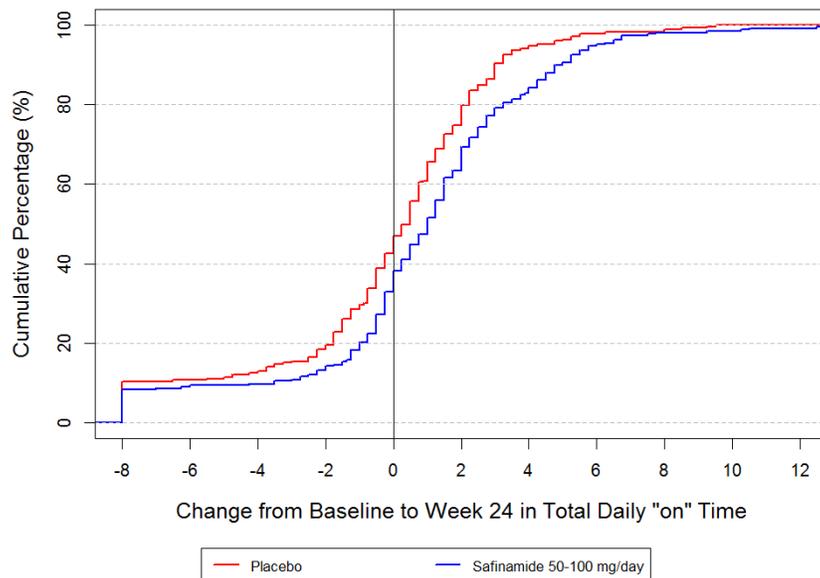


Figure 4. Study 27919 empirical cumulative distribution functions for the change from Baseline to Week 24 in total daily "on" time



The study populations in Study 016 and SETTLE were largely outside the United States (some N. America in SETTLE), were primarily Asian in Study 016, about 80% and about 67% Caucasian in SETTLE. About 35% of patients were over 65 in the 2 studies and about 35% were female. Analysis of results by age, race, gender, and geographic region by Dr. Zhang (p 24-30) did not find persuasive evidence of subgroup differences.

V. Safety

The clinical safety database is well-described by Drs. Bastings, Podskalny, and Kapcala, and I have little to add. There was adequate patient exposure (1949 with some exposure, 744 in open label studies for ≥ 12 months and almost 500 patients for > 2 years). In the controlled trials of late PD, discontinuations for adverse events were about 5% on drug and placebo and death rates were low and similar, 5/721 on safinamide and 3/497 on placebo. Open-label extensions did not identify unexpected deaths.

Serious adverse effects in controlled trials were largely similar in safinamide and placebo groups. The adverse reaction most clearly increased in rate on safinamide in controlled trials was dyskinesia (21% and 17% on 50 mg and 100 mg respectively, vs 9% on placebo. Falls, nausea and insomnia were slightly more common than placebo on 100 mg but not on 50 mg.

Retinal degeneration (atrophy of the outer nuclear layer) was observed in toxicology studies of up to 2-years' duration in rats and in a 2-year study in mice, but not in monkeys. In the 2-year study in rats, retinal scarring and cataracts were also observed. These findings led to close ophthalmological monitoring of patients in clinical trials. Although no signal of eye damage was observed and efforts were made to mask the reader of Optical Coherence Tomography (OCT) and electroretinography (ERG), the data, as assessed by Dr. Chambers, our ophthalmology consultant, are limited by missing data and limited numbers of examinations. The conclusion is that the available data neither rule out nor confirm the retinal degeneration observed in non-clinical studies. It is also noted that use of other PD medications, retinal disease associated with PD, and lack of good baseline data all confound interpretation. The animal data will be described in labeling in Warnings and Precautions, with a recommendation to monitor patients who have any history of retinal disease.

The resubmission included post-marketing European safety data involving about 10,000 patients. The safety results are considered in Dr. Podskalny's review. Of particular interest was a case of swollen tongue, dyspnea, gingival redness and swelling, rash on trunk, pruritus, hyperhidrosis, dry mouth and hoarseness, i.e., a hypersensitivity reaction. Symptoms resolved 4 days after drug withdrawal. The drug was re-initiated after one month off treatment, and the symptoms recurred after an additional month on the drug. This was considered angioedema, a dangerous effect and 2 cases of facial edema were identified in clinical studies. Labeling will contraindicate use in patients who develop angioedema on safinamide.

A metabolite of safinamide (NW 1689) inhibits BCRP (Breast Cancer Resistance Protein), an intestinal protein metabolizer of many potentially toxic (if concentrations were materially increased) drugs, including methotrexate, mitoxantrone, imatinib, and others. The IC₅₀ of NW 1689 is 3.7 μ M, a concentration achieved in PD patients given 100 mg/day. There will be, as suggested by the Office of Clinical Pharmacology, a post-marketing requirement (PMR) for the applicant to complete an interaction study, evaluating the effect of NW 1639 on blood levels of BCRP metabolized drugs. Labeling will note the need to monitor patients receiving safinamide with these drugs.

Safinamide causes embryofetal developmental toxicity when given to pregnant rats and rabbits. In both species, toxicity was more severe when safinamide was given with levodopa/carbidopa; in rabbits, unique fetal abnormalities were observed with the combination. Labeling will caution against use in pregnancy, obviously very unusual in patients with PD.

VI. Advisory Committee Meeting

Safinamide is the third selective MAO-B inhibitor approved in the US (after rasagiline and selegiline) for an identical population. No safety or effectiveness concerns needed advisory committee input.

VII. Drug Abuse Potential

The Controlled Substance Staff has concluded that safinamide did not show abuse potential in the non-clinical studies or the clinical studies. It is therefore not recommended for scheduling under the Controlled Substance Act (CSA). There do, however, appear to be some suggestions of withdrawal symptoms, and these should be noted as a warning regarding discontinuation in Dosage and Administration. The applicant should continue to monitor for signs of abuse of the drug and report on monitoring results.

VIII. Conclusion/Risk-Benefit/Action

The applicant has demonstrated the effectiveness of safinamide in increasing "ON" time in patients with mid-to-late-stage PD on levodopa in two well-controlled studies using 50 or 100 mg/day and will be approved for that use. There was also a statistically significant decrease in "OFF" time and improvement in the UPDRS Part III score (assessing motor symptoms) and these effects will be described in Section 14 of labeling. The effect was generally similar to previously approved selective monoamine oxidase type B inhibitors and adverse effects were also similar, the most frequent being dyskinesia. Adverse effects are reversible and monitorable and the increase in "ON" time, decrease in "OFF" time, and improvement in UPDRS III clearly outweigh the adverse effects. Labeling will also warn of typical MAO-B inhibitor effects (hypertension, serotonin syndrome, abrupt sleepiness, impulse control problems, and compulsive behavior). There is only weak evidence that the 100-mg dose is better than 50 mg, but there was a numerically greater effect of the higher dose on UPDRS Part III, an overall measure of motor symptoms, and tolerability was not notably worse. Both doses are therefore included in labeling. As noted above, non-clinical data have raised a concern about retinal effects, but human data did not confirm the concern. It will be noted in labeling.

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/s/

ROBERT TEMPLE
03/21/2017