Formulary Drug Review: Safinamide

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Danial E. Baker¹ and Anne P. Kim²

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Generic Name: Safinamide

Proprietary Name: *Xadago* (US WorldMeds, LLC)

Approval Rating: 1S

Therapeutic Class: Selective Monoamine Oxidase Type B Inhibitors, Sodium/Calcium/Glutamate Inhibitors

Similar Drugs: Rasagiline, Selegiline

Sound-/Look-Alike Names: Niacinamide, Rufinamide

Indications

Safinamide is approved by the US Food and Drug Administration (FDA) as adjunctive treatment to carbidopa/levodopa in patients with Parkinson disease experiencing “off” episodes.^{1,2}

Safinamide has not been shown to be effective as monotherapy for the treatment of Parkinson disease.²

Table 1 provides a comparison of the approved indications for the selective, reversible inhibitors of the enzyme monoamine oxidase type B (MAO-B) approved for the treatment of Parkinson disease.²⁻⁴

Clinical Pharmacology

Parkinson disease is mainly treated with medications that increase dopamine levels, such as levodopa and dopamine agonists.⁵ Due to the progressive nature of the disease, higher doses and/or combination therapy with levodopa and dopamine agonists are eventually required, and increased exposure to these medications can result in undesirable adverse reactions (eg, dyskinesia).⁵⁻⁸ Studies conducted in animals indicate that safinamide is a potent neuroprotectant with anticonvulsant and antiparkinsonian activity.⁹⁻¹³

Safinamide is a selective, reversible inhibitor of the enzyme MAO-B.^{9,13,14} Doses ranging from 25 to 600 µg/kg were administered to healthy male volunteers to obtain a dose-response curve of MAO-B inhibition. Safinamide has

an MAO-B inhibition median effective dose (defined as the dose at which enzyme activity is inhibited by 50% in 50% of treated subjects) of 87.54 µg·g/kg.^{9,13} Safinamide is approximately 5000 times more selective for MAO-B than MAO-A in rats and approximately 1000 times more selective in humans.¹⁴ By inhibiting this enzyme from metabolizing dopamine, safinamide increases the levels of dopamine available in the brain.¹⁵

In addition, safinamide is a sodium and calcium channel blocker, which leads to the inhibition of glutamate release.¹⁶ Because glutamate may play a role in development of dyskinesia, safinamide may have therapeutic benefit in reducing the incidence of dyskinesia, in addition to increasing dopamine concentrations.⁷

Safinamide did not prolong the QTc interval at a dose 3.5 times the maximum recommended dose.²

Pharmacokinetics

Safinamide exhibits linear pharmacokinetics from doses of 2.5 to 10 mg/kg. When healthy volunteers were exposed to safinamide doses of 2.5, 5, and 10 mg/kg, plasma levels increased linearly and proportionally in a dose-dependent manner.¹³

When safinamide is given intravenously (IV), the time to peak plasma concentration (T_{max}) is 0.5 hours.¹⁷ The T_{max} is 1.5 to 3 hours without food.^{2,13,15,17,18} A second safinamide T_{max} occurs 7 to 8 hours postexposure; this second peak may be associated with metabolites leaving tissues into which

¹Washington State University, Spokane, USA

²Washington State University, Yakima, USA

Corresponding Author:

Danial E. Baker, Director, Drug Information Center, and Professor of Pharmacotherapy, College of Pharmacy, Washington State University, PO Box 1495, Spokane, WA 99210-1495, USA.
Email: danial.baker@wsu.edu

Table 1. Comparison of the Selective, Reversible MAO-B Inhibitors Approved for the Treatment of Parkinson Disease.²⁻⁴

	Rasagiline	Safinamide	Selegiline
Trade name (manufacturer)	Azilect (Teva Pharmaceuticals)	Xadago (US WorldMeds)	Eldepryl, Zelapar (Various)
Generic available	Yes	No	Yes
FDA approval year	2006	2017	1996
Dosage forms available	Tablets	Tablets	Capsules, tablets, orally disintegrating tablets
Indication	Treatment of Parkinson disease as monotherapy or as adjunct therapy with or without levodopa	Treatment of Parkinson disease in patients experiencing "off" episodes, as adjunctive therapy to carbidopa/levodopa	Treatment of Parkinson disease as adjunct therapy to carbidopa/levodopa
Mechanism of action	MAO-B inhibitor	MAO-B inhibitor; sodium/calcium/glutamate inhibitor	MAO-B inhibitor

Note. MAO-B = monoamine oxidase type B; FDA = Food and Drug Administration.

they were originally distributed as the parent safinamide compound.¹⁸

Taking safinamide with food slows absorption ($T_{\max}$ 3.25–4.83 hours). However, food did not affect area under the curve (AUC) or maximum plasma concentration.^{2,13,17} The absolute bioavailability of safinamide is 95%, and first-pass metabolism is negligible.¹⁷

Safinamide is distributed well into tissues. The volume of distribution is 165 L.^{2,15,18} Plasma protein binding is 88% to 89%.²

Safinamide does not inhibit cytochrome P450 (CYP-450) 2C9, 2C19, 2D6, 2E1, and 3A4 isoforms. It does inhibit CYP1A1/2 to a negligible extent.¹³

Safinamide undergoes extensive hepatic metabolism, with only approximately 5% of the drug eliminated unchanged, mainly in the urine.^{2,15} Major enzymes involved in the metabolism of safinamide are MAO-B, amidase, aldehyde dehydrogenase, and uridine diphosphate–glucuronosyltransferase, with minor contributions from CYP3A4 and 2C19.^{2,15}

Metabolism of safinamide results in the major forms N-dealkylated acid and deaminated acid, and in the minor forms N-dealkylated glycine conjugate and 2-[4-hydroxybenzylamino]-propanamide. None of these metabolites have been shown to be therapeutically active compounds.^{2,17,18} While the half-life of safinamide is 20 to 26 hours, the half-life of circulating safinamide metabolites is longer (about 80 hours).^{2,18}

Clearance is 4.6 to 5.8 L/h after oral exposure and 4.8 L/h after IV exposure.^{2,15,17,18} Clearance of safinamide and its metabolites occurs mainly via the kidneys (76% to 84%).^{2,15,18}

Steady-state levels for safinamide are reached in 5 to 6 days, with a corresponding half-life of 20 to 26 hours.^{2,13,15,18} The half-life of safinamide is not affected by the route of administration; exposure to oral safinamide (taken with or without food) and IV safinamide both resulted in a half-life of 26 hours.¹⁷

Comparative Efficacy

Indication: Add-On Therapy for Management of Parkinson Disease

Guidelines

Guideline: The scientific and clinical basis for the treatment of Parkinson disease

Reference: Olanow CW, et al, 2009¹⁹

Comments: The guideline recommends starting a neuroprotective agent at the time of diagnosis. Drugs that have demonstrated neuroprotective effects include selegiline, rasagiline, coenzyme Q10, pramipexole, and ropinirole; however, no agents have conclusively demonstrated neuroprotective or disease-modifying effects in Parkinson disease to date. The guideline also recommends starting an agent for symptomatic therapy at the time of diagnosis or soon thereafter. Levodopa is the agent most commonly used for symptom management of Parkinson disease and others include dopamine agonists (eg, pramipexole, ropinirole), catechol-O-methyltransferase (COMT) inhibitors (eg, entacapone), MAO-B inhibitors (eg, selegiline, rasagiline), amantadine, and anticholinergics. Safinamide is mentioned in the guidelines as a promising agent for symptomatic therapy because it is the only MAO-B inhibitor studied as an add-on to levodopa and/or dopamine agonists.

Studies

Drug: Safinamide vs Placebo

Reference: Stocchi F, et al, 2004²⁰

Study Design: Randomized, double-blind, placebo-controlled, multicenter, dose-ranging study

Study Funding: Newron Pharmaceuticals

Patients: 167 patients 30 to 72 years of age with idiopathic Parkinson disease (Hoehn and Yahr stage I or II) for a maximum of 5 years. Patients who were treatment

naive or receiving 1 dopamine agonist (at a stable dose for at least 4 weeks) were eligible; 60.5% of patients were receiving a dopamine agonist. Patients were excluded if they had a history of alcohol or drug abuse, any motor fluctuations, present or past mental illness, Mini-Mental State Examination (MMSE) score of less than 24, Hamilton Depression Scale (HAMD) score of more than 17, or laboratory values outside of normal limits by more than 50%.

Intervention: Patients were randomized 1:1:1 to receive safinamide 0.5 mg/kg ($n = 55$), safinamide 1 mg/kg ($n = 56$), or placebo ($n = 56$) once daily after being weighed. All patients received 5 identical capsules each day at 8:00 AM for 12 weeks. The dopamine agonist dose was maintained at the preenrollment dose or, if necessary, was decreased during treatment.

Results

Primary End Point(s)

- Percentage of patients with at least 30% improvement in Unified Parkinson Disease Rating Scale (UPDRS) part III (motor examination) scores was 30.9% in the 0.5 mg/kg group, 37.5% in the 1 mg/kg group, and 21.4% in the placebo group.

End Point(s)

- Percentage of patients with at least 30% improvement in UPDRS part III in the subpopulation taking safinamide and a dopamine agonist ($n = 101$): 36.4% in the 0.5 mg/kg group, 47.1% in the 1 mg/kg group, and 20.6% in the placebo group.

Comments: The average safinamide dose was 40 mg (range, 20–40 mg) for the 0.5 mg/kg group and 70 mg (range, 40–90 mg) for the 1 mg/kg group. The combination of safinamide and a dopamine agonist resulted in increased benefit. There were no tolerability issues with the highest dose of safinamide, which allows for the use of higher doses in future studies.

Limitations: The purpose of this study was to determine whether safinamide improves Parkinson disease symptoms. The sample size was not powered for any end point. It is unclear in which countries this study was conducted.

Reference: Stocchi F, et al, 2012 (Study 015)⁸

Study Design: Randomized, double-blind, placebo-controlled, parallel-group, multicenter study

Study Funding: Newron Pharmaceuticals, Merck Serono

Patients: 269 patients with idiopathic Parkinson disease (Hoehn and Yahr stage I to III) for less than 5 years. Patients were required to be on a stable dose of a single dopamine agonist for at least 4 weeks before screening. At baseline, average patient age was 57.4 years; 63% were

male; 59% were white and 37% Asian; and average duration of Parkinson disease was 2.5 years. Clinical Global Impression–Severity of Illness (CGI-S) score was approximately 3.1, UPDRS part III (motor examination) score was 20.7, MMSE score was approximately 28.5, and HAMD score was approximately 4.2, with no meaningful differences among treatment groups. The majority of dopamine agonist use included ropinirole (45% to 48%), pramipexole (23% to 30%), bromocriptine (11% to 22%), and cabergoline (3%–10%). Exclusion criteria were end-of-dose “wearing off,” “on/off” phenomena, disabling dysmnnesia, or wide fluctuations; severe postural hypotension; concomitant use of monoamine oxidase inhibitors (MAOIs); or use of other Parkinson disease medications other than the single dopamine agonist.

Intervention: Patients were randomized 1:1:1 to receive safinamide 100 mg ($n = 90$), safinamide 200 mg ($n = 89$), or placebo ($n = 90$) once daily with breakfast for 24 weeks. All patients were maintained on their preenrollment dose of dopamine agonist throughout the study; however, for patients receiving the maximum dose of study medication and whose motor symptoms were worsening, the dopamine agonist dose could be increased or other Parkinson disease medications added.

Results

Primary End Point(s)

- Average difference from baseline to week 24 in UPDRS part III scores in the intention-to-treat (ITT) population (eg, all patients who received at least 1 dose), without imputation for missing data, was -6 with safinamide 100 mg (-1.9 point estimate vs placebo [95% confidence interval, CI, -3.7 to -0.1 ; $P = .0419$]), -3.9 with safinamide 200 mg (-0.4 point estimate vs placebo [95% CI, -2.3 to 1.4 ; $P = .65$]), and -3.6 with placebo.

Secondary End Point(s)

- Percentage of patients with response at week 24:
 - Clinical Global Impression–Change (CGI-C) score (response defined as a score between 1 and 3): approximately 61% in the safinamide 100 mg group ($P = .18$ vs placebo), approximately 59% in the safinamide 200 mg group ($P = .08$ vs placebo), and approximately 49% in the placebo group.
 - UPDRS part III score (response defined as having at least 30% improvement with no deterioration in part II [activities of daily living] and part IV [complications of therapy] scores): approximately 38% with 100 mg ($P = .05$), approximately 36% with 200 mg ($P = .08$), and approximately 24% with placebo.

- Average change in UPDRS part II score from baseline to week 24 was -2.2 with safinamide 100 mg ($P = .0248$ vs placebo), -1.4 with safinamide 200 mg (no difference vs placebo), and -1.2 with placebo.
- No significant differences were observed in change from baseline to 24 weeks for HAMD, UPDRS part I, UPDRS part IV, and MMSE scores.

Comments: The study targeted a patient population with early-stage Parkinson disease. The majority (more than 90%) of the patients received their target dose of 100 or 200 mg/d. Secondary end points were analyzed via ITT analysis (using the last observation carried forward [LOCF] method) and via observed case analysis. Blood samples taken at weeks 8 and 12 revealed safinamide contamination in the placebo group: 2 bulk bottles of unknown quantity that were supposed to be placebo capsules contained both placebo and safinamide capsules. The investigators determined that this unintended exposure did not greatly affect the results because the safinamide plasma concentrations obtained from the patients in the placebo group were consistently less than 20% of the measured safinamide concentrations obtained from patients in the safinamide 100 mg group. Reasons for discontinuing study drug included withdrawal of consent (approximately 6.3%) and nonserious adverse events (approximately 3%). Patients who completed this study were invited to enroll in a 12-month blind extension study.⁵

Limitations: It is unknown to what degree the low level of exposure to safinamide in the placebo group impacted outcomes. This study was not conducted in the United States; subjects were recruited from Italy, Spain, the United Kingdom, India, Argentina, Chile, and Colombia.

Reference: Schapira A, et al, 2013 (Study 017)⁵

Study Design: Randomized, double-blind, placebo-controlled, parallel-group, multicenter extension study (extension of the 24-week Study 015)

Study Funding: Newron Pharmaceuticals, Merck Serono

Patients: 227 of the 269 patients with idiopathic Parkinson disease (Hoehn and Yahr stage I to III) for less than 5 years from 24-week Study 015 (Stocchi et al, 2012) entered this 12-month extension study. Patients were included if they had completed the 24-week study and demonstrated adherence to treatment, or if they had not completed the study but completed all evaluations. Patients were required to be on a stable dose of a single dopamine agonist for at least 4 weeks before screening. At baseline, median patient age was 57.7 years; 63.4% were male; and average duration of Parkinson disease was 2.5 years. Mean UPDRS part II (activities of daily living) score was approximately 8.1, UPDRS part III (motor examination) was approximately 21.3, MMSE score was approximately 28.5, and HAMD score was approximately 4.2, with no meaningful differences among treatment

groups. The majority of dopamine agonist use included ropinirole (44.9%-48.8%), pramipexole (16.3%-24.6%), and cabergoline (1.4%-10%).

Intervention: Patients continued receiving the medication they were randomized to in the primary study (safinamide 100 mg [$n = 80$], safinamide 200 mg [$n = 69$], or placebo ($n = 78$)) once daily with breakfast for 12 months. All patients were maintained on their preenrollment dose of dopamine agonist throughout the study; however, for patients whose Parkinson disease symptoms worsened, the dopamine agonist dose could be increased or other Parkinson disease medications added.

Results

Primary End Point(s)

- In the ITT population, the median number of days from the first day of the 24-week study to intervention (eg, increasing the dopamine agonist dose or adding another Parkinson disease medication) was greater for the safinamide 100 and 200 mg groups combined (559 days) compared with the placebo group (466 days), but this difference was not statistically significant ($P = .33$).

Secondary End Point(s)

- Percentage of patients requiring intervention was 39.7% of the pooled safinamide groups and 47.8% of the placebo group (not statistically significant).
- Mean changes from baseline in UPDRS, CGI-C, CGI-S, or Hoehn and Yahr scores were not significantly different between the pooled safinamide groups and placebo.

End Point(s)

- Mean changes from baseline for MMSE or HAMD scores were not significantly different.

Comments: In this 12-month extension of a 24-week study, safinamide at the doses evaluated was not superior to established dopamine agonist treatments already available for Parkinson disease. The extension study was completed by 82% of patients. Because the primary end point was a time-to-event outcome (results shown on Kaplan-Meier curves), no imputation method was necessary for missing data. However, secondary and tertiary end points were analyzed via ITT analysis, using the LOCF method for any missing data. Reasons for discontinuing study drug included withdrawal of consent (approximately 7%) and lack of efficacy (approximately 4.8%).

Limitations: This study was not conducted in the United States; subjects were recruited from Italy, Spain, the United Kingdom, India, Argentina, Chile, and Colombia.

Drug: Safinamide plus Levodopa vs Placebo plus Levodopa

Reference: Borgohain R, et al, 2014 (Study 016)⁶

Study Design: Randomized, double-blind, placebo-controlled, parallel-group, multicenter study

Study Funding: Newron Pharmaceuticals, Merck Serono

Patients: 669 patients with idiopathic Parkinson disease (Hoehn and Yahr stage I to IV) stabilized on levodopa for at least 4 weeks. Patients' disease was marked by a period of more than 1.5 h/d of "off" time (referring to times of decreased mobility, whereas "on" time refers to times during which medication therapy controls Parkinson disease symptoms). Individual diaries of "on" and "off" times had to be maintained. At baseline, average patient age was 60 years; 71.7% were male; 19.4% were white and 80.6% Asian; and average duration of Parkinson disease was 8 years. Mean UPDRS part III score was approximately 28, with no meaningful differences among treatment groups. Concomitant Parkinson disease medications included dopamine agonist (approximately 60.8%), entacapone (approximately 24.4%), anticholinergic (approximately 37.1%), and/or amantadine (approximately 13.9%). Patients were excluded if they had severe, disabling peak-dose or biphasic dyskinesia or unpredictable or wide fluctuations; or evidence of dementia, major psychiatric illnesses, and/or severe progressive medical illnesses.

Intervention: Patients were randomized 1:1:1 to receive safinamide 50 mg ($n = 223$), safinamide 100 mg ($n = 224$), or placebo ($n = 222$) once daily with breakfast for 24 weeks. All patients were maintained on their preenrollment dose of levodopa throughout the study; however, the levodopa dose could be increased or other Parkinson disease medications (except MAO-B inhibitors) added as rescue therapy.

Results

Primary End Point(s)

- In the ITT population, least squares (LS) mean change from baseline to week 24 in total daily "on" time with no to nontroublesome dyskinesia was 1.23 hours with safinamide 50 mg (LS mean change vs placebo of 0.51 hours [95% CI, 0.07-0.94; $P = .0223$]), 1.26 hours with safinamide 100 mg (LS mean change vs placebo of 0.55 hours [95% CI, 0.12-0.99; $P = .013$]), and 0.8 hours with placebo.

Secondary End Point(s)

- Average total daily "off" time at week 24 was 3.9 hours with safinamide 50 mg, 3.9 hours with safinamide 100 mg, and 4.6 hours with placebo. The average LS mean difference versus placebo was -0.6 (95% CI, -0.9 to -0.2 ; $P = .0043$) for safinamide 50 mg and -0.6 (95% CI, -1 to -0.2 ; $P = .0034$) for

safinamide 100 mg. Average "off" time following the morning dose of levodopa at week 24 was 3.6 hours with safinamide 50 mg, 3.5 hours with safinamide 100 mg, and 4.2 hours with placebo. The average change in "off" time following the levodopa dose from baseline to week 24 was -1.1 with safinamide 50 mg ($P = .0031$), -1.2 with safinamide 100 mg ($P = .0011$), and -0.6 with placebo.

- Average difference between baseline and week 24 UPDRS part III (motor examination) score was -6.1 with safinamide 50 mg (LS mean change vs placebo of -1.8 [95% CI, -3.3 to -0.4 ; $P = .0138$]), -6.9 with safinamide 100 mg (LS mean change vs placebo of -2.6 [95% CI, -4.1 to -1.1 ; $P < .001$]), and -4.3 with placebo. Average change in UPDRS part II (activities of daily living) score from baseline was only significant for the 100 mg group (-2.2 ; $P = .006$ vs placebo).
- Percentage of patients showing improvement in CGI-C scores at week 24 was 66.4% in the 50 mg group ($P = .001$ vs placebo), 64.3% in the 100 mg group ($P = .0089$), and 55.4% in the placebo group. Average change in CGI-S score from baseline to week 24 was -0.4 with safinamide 50 mg ($P = .006$ vs placebo), -0.4 with safinamide 100 mg ($P = .0448$ vs placebo), and -0.2 with placebo.
- No significant between-group differences were observed in changes from baseline to week 24 in Dyskinesia Rating Scale (DRS) scores during "on" time or in levodopa dose reduction percentages.

End Point(s)

- Average change from baseline in Parkinson Disease Questionnaire (PDQ-39) subscale score was significant for emotional well-being, communication, and bodily discomfort in the 100 mg group. The other subscale scores (reflecting mobility, stigma, social support, and cognition) were not statistically different from placebo score changes.
- No significant differences were observed in mean change from baseline for HAMD score in both groups.

Comments: The study targeted a patient population with mid- to late-stage Parkinson disease. The majority of patients (87%-90%) remained at their preenrolled dose of levodopa throughout the study. Eighty-nine percent of the enrolled patients completed the study. More patients in the placebo group reported increased Parkinson disease symptoms and depression, while more patients in the safinamide groups reported increased dyskinesia. Reasons for discontinuing study drug included nonserious adverse events (3.9%) and withdrawal of consent (2.7%).

Limitations: This study was not conducted in the United States; subjects were recruited from India (80.6%), Romania (15.8%), and Italy (3.6%).

Reference: Borgohain R, et al, 2014 (Study 018)⁷

Study Design: Randomized, double-blind, placebo-controlled, parallel-group, multicenter extension study (extension of 24-week Study 016)

Study Funding: Newron Pharmaceuticals, Merck Serono

Patients: 544 of the 669 patients with idiopathic Parkinson disease from the 24-week Study 016 entered this 18-month extension study. Patients were included if they had completed Study 016 and demonstrated adherence to treatment, or if they had not completed the study but completed all evaluations. The only baseline characteristic provided from this study's ITT population was a mean DRS score of 3.7; all other baseline characteristics provided were from the previously described 24-week study. Patients were excluded if they had experienced clinically significant adverse events or shown clinically significant deterioration in motor symptoms during the 24-week study. The following concomitant medications were prohibited: serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic or tetracyclic antidepressants, neuroleptics, MAO-B inhibitors, tramadol, meperidine, and agents that inhibit or induce hepatic enzymes.

Intervention: Patients were randomized 1:1:1 to receive safinamide 50 mg (n = 189), safinamide 100 mg (n = 180), or placebo (n = 175) once daily with breakfast for 18 months. All patients were maintained on their pre-enrollment dose of levodopa throughout the study; however, other Parkinson disease medications could be added for patients whose Parkinson disease symptoms worsened.

Results

Primary End Point(s)

- LS mean difference in DRS score during "on" time from the first day of the 24-week study to the last day of the 24-month study was -0.51 (95% CI, -1.32 to 0.29; not significant [NS]) with safinamide 50 mg and -0.59 (95% CI, -1.4 to 0.21; NS) with safinamide 100 mg.

Secondary End Point(s)

- LS mean change in "on" time at the end of the study was 1.01 hours (95% CI, 0.23 to 1.11; $P = .0031$) with safinamide 50 mg, 1.18 hours (95% CI, 0.39 to 1.27; $P < .001$) with safinamide 100 mg, and 0.34 hours with placebo.
- Reduction in levodopa dose at the end of the study was 17% in the safinamide 50 mg group, 18.3% in the safinamide 100 mg group, and 11.3% in the placebo group.
- No data were provided, but statistically significant improvements in the following end points were indicated: "on" time without dyskinesia or troublesome dyskinesia, "off" time, and CGI-S scores for both the safinamide 50 and 100 mg groups; UPDRS parts II to

IV scores, PDQ-39 total score, and GRID-HAMD score for the safinamide 100 mg group; and CGI-C scores for the safinamide 50 mg group.

Comments: In this 18-month extension of a 24-week study, safinamide was not superior to established treatments already available for Parkinson disease. Eighty-one percent of enrolled patients completed the extension study. An ad hoc analysis of 242 patients who had a baseline DRS of more than 4 was performed. Findings of significance are likely due to chance because the subpopulations of 86 patients in the safinamide 50 mg group, 80 patients in the safinamide 100 mg group, and 76 patients in the placebo group were small. Safety analysis revealed that safinamide was more frequently associated with dyskinesia than placebo (31.2% with safinamide 50 mg and 27.8% with safinamide 100 mg vs 21.7% with placebo), but it is unclear to what extent levodopa contributed to the development of dyskinesias. Reasons for discontinuing study drug included withdrawal of consent (8.1%) and loss to follow-up (3.3%). A post hoc analysis of the extension study found that safinamide 100 mg/d improved the DRS score compared with placebo in the subgroup of patients with no change in levodopa dose ($P = .0488$) and in patients with baseline dyskinesia ($P = .0153$) with or without changes in levodopa dose.²¹

Limitations: This study was not conducted in the United States; subjects were recruited from India, Romania, and Italy.

Reference: Schapira AHV, 2017 (SETTLE trial)²²

Study Design: Randomized, double-blind, multicenter study

Study Funding: Newron, Merck Serono

Patients: 549 patients 30 to 80 years of age with idiopathic Parkinson disease longer than 3 years' duration and a daily "off" time greater than 1.5 hours (excluding morning akinesia). All patients had to be levodopa responsive and be following a stable levodopa regimen (3-10 doses per day of any levodopa preparation, with or without a COMT inhibitor) for 4 weeks. Additional allowed anti-parkinson drugs included dopamine agonists, anticholinergics, COMT inhibitors, and/or amantadine at a stable dose. Patients were excluded for severe, disabling peak-dose or biphasic dyskinesia and/or wide or unpredictable symptom fluctuations. Prior MAO-B inhibitors had to be discontinued at least 8 weeks before screening. Baseline characteristics were well balanced between the 2 treatment groups: mean age was 61.9 years; 60.8% were male; 67.6% were white and 31% Asian; and 40% were from Western Europe, 31% were from the Asia-Pacific region, 19% were from North America, and 11% were from Eastern Europe. Mean levodopa dose was 760.8 mg/d in the safinamide group and 792.3 mg/d in the placebo group. Mean duration of Parkinson disease was 8.9 years.

Intervention: Background antiparkinson drugs were adjusted to minimize motor fluctuation during a 10-day screening period. Patients were then observed on the stable dose for a minimum of 4 weeks, at the end of which they were still required to be experiencing daily “off” time of greater than 1.5 hours. The randomized portion of the study began after the screening and observation periods. Patients were randomized (1:1) to receive either safinamide 50 mg/d or placebo as 1 tablet once daily with breakfast for 24 weeks. If there were no tolerability issues by day 14, the starting dosage of safinamide (50 mg/d) was increased to 100 mg/d; at day 14, 90.9% in the safinamide group and 94.1% in the placebo group were prescribed the 100-mg target dose. If an upward increase in dose of any of the other antiparkinson drugs was necessary prior to week 24, the assessment used for the primary efficacy end point was conducted prior to the dosage adjustment. If patients completed the 24-week study, they were eligible for enrollment in an open-label extension study.

Results

Primary End Point(s)

- Change in mean daily “on” time without troublesome dyskinesia from baseline to week 24, as recorded by patients or caregivers in a diary recording each 30-minute interval during the 18-hour day (0600 to 2400 hours) as “on” time, “on” time with nontroublesome dyskinesia, “on” time with troublesome dyskinesia, “off” time, or time asleep: Mean increase in total daily “on” time without troublesome dyskinesia was 1.42 hours in the safinamide group and 0.57 hours in the placebo group (LS mean difference, 0.96 hours; 95% CI, 0.56-1.37; $P < .001$). In the mixed-effects repeated-measures model, the mean increases were 1.61 and 0.17 hours, respectively (LS mean difference, 0.93 hours; 95% CI, 0.5-1.36; $P < .001$).

Secondary End Point(s)

- Mean decrease in daily “off” time was -1.56 hours in the safinamide group and -0.54 hours in the placebo group (LS mean difference, -1.03 hours; 95% CI, -1.4 to -0.67 ; $P < .001$).
- Mean decrease (improvement) in UPDRS part III (motor examination) score, rated during an “on” phase, was -3.43 in the safinamide group and -1.83 in the placebo group (LS mean difference, -1.82 ; 95% CI, -3.01 to -0.62 ; $P = .003$); and mean change in UPDRS part II (activities of daily living) score was -1.07 and -0.75 , respectively (LS mean difference, -0.43 ; 95% CI, -1.02 to 0.16 ; $P = .15$).

- Nominal differences were also observed for change in CGI-C rating, CGI-S rating, Patient Global Impression–Change rating, PDQ-39 score, and EuroQoL 5 dimensions (EQ-5D) score.
- Change in levodopa daily dosage was -1.11% in the safinamide group and 0.78% in the placebo group (nominal $P = .02$).
- “Off” time after the morning levodopa dose was -0.26 hours in the safinamide group and -0.09 hours in the placebo group ($P < .001$ nominal).

Comments: This study was conducted in Europe, the Asia-Pacific region, and North America using an ITT population for the efficacy analysis. The 24-week study was completed by 89.4% of the safinamide group and 87.6% of the placebo group. Discontinuation of study drug and a change in antiparkinson treatment was necessary in 4.4% of the safinamide group and in 3.6% of the placebo group. Any missing data were imputed using the LOCF method. Background antiparkinson therapy consisted of dopamine agonist (74.3%), amantadine (30.2%), an anticholinergic (17.3%), and entacapone (15.1%). Statistical analysis was conducted using a hierarchical approach; if no statistical difference was found, further analyses were performed to obtain nominal P values. A sensitivity analysis was conducted, in which the change in daily “on” time was examined using a mixed-effects repeated-measures model, with no imputation of missing data. The safety analysis was performed using the modified ITT population (ie, those who received the study medication).

Post hoc analysis of the SETTLE trial and of Study 016 found that mean daily “on” time and “off” time improved, compared with placebo, to similar extents regardless of whether patients were receiving concomitant dopamine agonists, COMT inhibitors, or amantadine.²³ Another post hoc analysis of the same 2 studies suggests that safinamide may have a positive effect on the nonmotor symptom pain.²⁴

Limitations: The evaluation phase of the study was only 24 weeks.

Contraindications, Warnings, and Precautions

Contraindications

Safinamide is contraindicated with concomitant use of other drugs in the MAOI class or other drugs that are potent inhibitors of monoamine oxidase (eg, linezolid); opioid drugs (eg, meperidine and its derivatives, methadone, propoxyphene, tramadol); SNRIs; tricyclic, tetracyclic, or triazolopyridine antidepressants; cyclobenzaprine; methylphenidate, amphetamine, and their derivatives; St. John’s wort; and dextromethorphan.² Use with MAOIs or related drugs may result in

increased blood pressure. Use with opioid drugs, antidepressants, or other drugs with serotonin-related activity may result in life-threatening serotonin syndrome. Use with dextromethorphan may cause episodes of psychosis or abnormal behavior.²

Safinamide is also contraindicated in patients who have a history of a hypersensitivity (eg, swelling of the tongue and oral mucosa, dyspnea) to safinamide.² A potential contraindication is a history of hypersensitivity to other product ingredients (ie, colloidal silicon dioxide, crospovidone, hypromellose, iron oxide [red], magnesium stearate, microcrystalline cellulose, polyethylene glycol 6000, potassium aluminum silicate, and titanium dioxide).²

Safinamide is contraindicated in patients with severe hepatic impairment (Child-Pugh class C).²

Warnings and Precautions

Hypertension or exacerbation of existing hypertension may occur during safinamide therapy. Monitor patients for new-onset hypertension or for hypertension not adequately controlled after starting safinamide. Concomitant use with sympathomimetic drugs may increase blood pressure. Medication adjustment may be necessary if elevated blood pressure is sustained.² Dietary tyramine restriction is not required during treatment with recommended doses of safinamide, except with certain foods containing very high amounts (ie, more than 150 mg) of tyramine, which may increase blood pressure.² Concurrent use with isoniazid may also be associated with the potential for increased blood pressure.²

Potentially life-threatening serotonin syndrome may occur when patients receiving an MAOI (including selective MAO-B inhibitors) receive concomitant treatment with SNRIs; tricyclic, tetracyclic, or triazolopyridine antidepressants; cyclobenzaprine; opioid drugs (eg, meperidine and meperidine derivatives, propoxyphene, tramadol); or methylphenidate, amphetamine, and their derivatives. Use of safinamide with any of these drugs is contraindicated.²

Concomitant use of selective serotonin reuptake inhibitors (SSRIs) and safinamide has been associated with development of serotonin syndrome. If the patient requires treatment with an SSRI and safinamide, the lowest effective dose of the SSRI should be used.²

Use of dopaminergics has been associated with patients falling asleep while engaged in activities of daily living (eg, driving a motor vehicle, conversing, eating). Patients may not perceive warning signs (ie, excessive drowsiness), or they may report feeling alert immediately prior to the event. If sleep attacks/sudden onset of sleep does occur, discontinuation is recommended. If safinamide treatment is continued, the patient should be advised not to drive or engage in other potentially dangerous activities.²

Dyskinesia or exacerbation of preexisting dyskinesia may occur. The condition may be mitigated by reducing the

patient's daily levodopa dosage or the dosage of another dopaminergic drug. Discontinuation of safinamide therapy in clinical trials due to dyskinesia occurred in 1% of patients receiving either dose of safinamide (50 mg or 100 mg).²

Patients with hallucinations or psychotic disorders are not ideal candidates for safinamide therapy. Increased central dopaminergic activity may cause an exacerbation of the patient's psychosis, and the mechanism of action of some antipsychotic medications may exacerbate the symptoms of Parkinson disease. If safinamide and antipsychotic medication are used together, a dosage reduction or discontinuation may be necessary if the patient develops hallucinations or psychotic-like behavior.²

Changes in impulse control/compulsive behavior (intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges) may occur in patients treated with drugs that increase central dopaminergic activity. The patient may not recognize any changes in behavior. If the patient develops such urges after the addition of safinamide to the drug regimen, a reduction in dose or discontinuation of safinamide may be necessary.²

Rapid dose reduction, or withdrawal of or changes in drugs that increase central dopaminergic activity may result in a symptom complex resembling neuroleptic syndrome.²

Retinal pathology (eg, retinal degeneration, loss of photoreceptor cells, retinal scarring, cataracts) was observed in rats administered safinamide. Patients should be evaluated periodically for changes in vision, especially if they have a history of retinal/macular degeneration, uveitis, inherited retinal conditions, family history of hereditary retinal disease, albinism, retinitis pigmentosa, or any active retinopathy (eg, diabetic retinopathy).²

There are no adequate and well-controlled studies of safinamide in pregnant women. In animal studies, developmental toxicity and teratogenic effects were observed.²

It is not known whether safinamide is present in human milk. Skin discoloration was observed in rat pups indirectly exposed to safinamide through milk. The change in skin color was thought to be related to hyperbilirubinemia resulting from hepatobiliary toxicity.²

The safety and effectiveness of safinamide in pediatric patients have not been established.²

Table 2 provides a comparison of contraindications, warnings, and precautions for the MAO-B inhibitors approved for the treatment of Parkinson disease.²⁻⁴

Adverse Reactions

The most common adverse reactions observed in clinical trials included dyskinesia (17%-21%), fall (4%-6%), nausea (3%-6%), and insomnia (1%-4%).^{2,5-8,25} Discontinuation occurred in 5% of patients receiving safinamide 50 mg/d, in 6% with safinamide 100 mg/d, and in 4% with placebo; the most frequent reason for discontinuation was dyskinesia.²

Table 2. Comparison of Contraindications, Warnings, and Precautions for the MAO-B Inhibitors Approved for the Treatment of Parkinson Disease.^{2,4}

	Rasagiline	Safinamide	Selegiline
Contraindications			
Hypersensitivity to the drug	^a	X	X
Concomitant use of other drugs in the MAOI class	X	X	^a
Concomitant use of other drugs that are potent inhibitors of monoamine oxidase (eg, linezolid); opioid drugs (eg, meperidine and its derivatives, methadone, propoxyphene, tramadol); SNRIs; tricyclic, tetracyclic, or triazolopyridine antidepressants; cyclobenzaprine; methylphenidate, amphetamine, and their derivatives; St. John's wort; or dextromethorphan	X	X	X
Use with MAOIs or related drugs may result in increased blood pressure	^a	X	X
Opioid drugs, antidepressants, or other drugs with serotonin-related activity may result in life-threatening serotonin syndrome	^a	X	X
Concomitant use with dextromethorphan	X	X	^a
Severe hepatic impairment (Child-Pugh class C)		X	
Warnings and precautions			
Changes in impulse control/compulsive behavior	X	X	X
Concurrent use of isoniazid may increase blood pressure		X	
Dyskinesia or exacerbation of preexisting dyskinesia	X	X	X
Hallucinations or psychotic disorders	X	X	^b
Hypertension or exacerbation of preexisting hypertension	X	X	X
Hypotension	X		
Melanoma	X		X
Retinal pathology (eg, retinal degeneration, loss of photoreceptor cells, retinal scarring, cataracts)		X	
Serotonin syndrome	X	X	X
Sleep attacks/sudden onset of sleep	X	X	^b
Symptom complex resembling neuroleptic syndrome	X	X	X
Tyramine-containing foods	X	X	X
Pediatric patients	Safety and efficacy not established	Safety and efficacy not established	Safety and efficacy not established

Note. MAOIs = monoamine oxidase inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors.

^aNot listed in the prescribing information, but should be considered a contraindication.

^bNot listed in the prescribing information, but should be considered a warning or precaution because these effects are related to its mechanism of action.

Drug Interactions

Most of the drug interactions associated with rasagiline, safinamide, and selegiline are related to their mechanism of action, to MAO-B inhibitors, or to the risk of serotonin syndrome.²⁻⁴

Safinamide is a selective MAOI; use of safinamide is contraindicated with use of other drugs in the MAOI class or with other drugs that are potent inhibitors of monoamine oxidase (eg, linezolid, an oxazolidinone antibiotic that also has reversible nonselective monoamine oxidase inhibiting activity). Coadministration increases the risk of nonselective monoamine oxidase inhibition, which may lead to hypertensive crisis. At least 14 days should elapse between discontinuation of safinamide and initiation of treatment with other MAOIs.²

Isoniazid has some monoamine oxidase-inhibiting activity, and if used with safinamide, the patient should be monitored for hypertension and reaction to dietary tyramine.²

Safinamide does not cause hypertensive crisis after IV or oral exposure to tyramine.^{9,14,26} In an open-label, single-dose, placebo-controlled, crossover phase 1 study of 8 male subjects, the average dose of IV tyramine needed to raise blood pressure by 30 mm Hg after receiving a single dose of placebo or a single dose of safinamide (2 mg/kg) was not significantly different (4.1 mg for placebo and 4.3 mg for safinamide).⁹ In another open-label, single-center, phase 1 study, exposure to oral tyramine (50-200 mg) after reaching steady state with safinamide 300 mg (after 5 days) did not cause a 30 mm Hg or higher increase in systolic blood pressure in 18 of 20 subjects (mean systolic blood pressure increase was 13.1 mm Hg with tyramine alone and 14.7 mm

Hg with safinamide plus tyramine).¹⁴ Exercise-induced systolic blood pressure changes (range, 20-52 mm Hg) were greater than the increases in systolic blood pressure observed after concomitant exposure to safinamide and tyramine.¹⁴ A randomized, double-blind, positive-controlled (phenelzine), comparator-controlled (selegiline), and double-dummy placebo-controlled study confirmed that oral exposure to tyramine while taking safinamide (100 mg or a supratherapeutic dose of 350 mg) did not produce a clinically significant increase in blood pressure.²⁶ However, the safinamide prescribing information recommends caution because the selectivity of safinamide is dose related above the highest recommended daily dosage; patients should be advised to avoid foods containing large amounts of tyramine (eg, aged, fermented, cured, smoked, and pickled foods containing large amounts of exogenous amines), even if they are receiving the recommended doses of safinamide.²

Serious, sometimes fatal reactions have been precipitated with concomitant use of safinamide with opioid drugs (eg, meperidine and its derivatives, methadone, propoxyphene, tramadol) and MAOIs, including selective MAO-B inhibitors. Concomitant use of safinamide with these drugs is contraindicated. At least 14 days should elapse between discontinuation of safinamide and initiation of treatment with these drugs.²

The use of some serotonergic drugs (ie, SNRIs; triazopyridine, tricyclic, or tetracyclic antidepressants; cyclobenzaprine; St. John's wort) with safinamide is contraindicated. At least 14 days should elapse between discontinuation of safinamide and initiation of treatment with these drugs.² Patients requiring treatment with SSRIs may be at risk of developing serotonin syndrome and should be closely monitored.²

The combination of MAOIs and dextromethorphan has been reported to cause episodes of psychosis or bizarre behavior. Due to safinamide's MAO inhibitory activity, concomitant use with dextromethorphan is contraindicated.²

Sympathomimetic medications used in combination with nonselective or selective MAOIs may cause severe hypertensive reactions, including hypertensive crisis. Concomitant use of safinamide with methylphenidate, amphetamine, and their derivatives is contraindicated. Caution is recommended if safinamide is prescribed concomitantly with prescription or nonprescription sympathomimetic medications, including nasal, oral, or ophthalmic decongestants and cold remedies.²

Safinamide and its major metabolite may inhibit intestinal breast cancer resistance protein (BCRP). Inhibition of BCRP could increase plasma concentrations of BCRP substrates (eg, methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan). Monitor patients for increased pharmacologic or adverse effects of BCRP substrates if safinamide is used concomitantly.²

Dopamine antagonists (eg, antipsychotics, metoclopramide) may decrease the effectiveness of safinamide and exacerbate the symptoms of Parkinson disease.²

The metabolism of safinamide is minimally affected by strong CYP-450 inhibitors.¹⁵ In a randomized, open-label, single-center, crossover study, 7 male and 7 female subjects were exposed to a single dose of safinamide 100 mg alone and a single dose of safinamide 100 mg on day 3 of a 6-day regimen of ketoconazole 200 mg twice daily. Treatments were separated by a washout period of at least 21 days. Plasma levels (C_{max} and AUC) of safinamide and its metabolites were not significantly different after taking safinamide alone compared with taking safinamide with ketoconazole, a strong CYP-450 inhibitor.¹⁵

Recommended Monitoring

Monitor for signs of worsening Parkinson disease symptoms and/or signs of dyskinesia; blood pressure; signs and symptoms of serotonin syndrome; and visual changes.^{2,6}

Dosing

The recommended starting dosage is safinamide 50 mg orally once daily at the same time of day and without regard to meals. After 2 weeks, the dosage may be increased to 100 mg once daily based on individual need and tolerability.² In patients with moderate hepatic impairment (Child-Pugh class B), the maximum recommended dose is 50 mg once daily. Use in patients with severe hepatic impairment (Child-Pugh class C) is contraindicated.²

Daily doses of safinamide above 100 mg have not been shown to provide additional benefit, and higher doses increase the risk for adverse reactions. Safinamide has been shown to be effective only in combination with carbidopa/levodopa.²

If safinamide therapy needs to be discontinued and the safinamide dosage is 100 mg/d, the dosage should be decreased to 50 mg/d for 1 week before discontinuation.²

Table 3 provides a comparison of dosing recommendations for the MAO-B inhibitors approved for the treatment of Parkinson disease.²⁻⁴

Product Availability

A New Drug Application was submitted to the FDA on May 29, 2014. The Prescription Drug User Fee Act date was originally set for May 2015.²⁷ Safinamide was approved by the FDA on March 21, 2017.¹

Safinamide is available as 50-mg and 100-mg round, film-coated, biconcave shaped tablets in bottles of 30 and 90. It should be stored at 25°C (77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F).²

Drug Safety/Risk Evaluation and Mitigation Strategy (REMS)

No REMS is required for safinamide.¹

Table 3. Comparison of Dosing Recommendations for the MAO-B Inhibitors Approved for the Treatment of Parkinson Disease.²⁻⁴

	Rasagiline	Safinamide	Selegiline
Initial dose	Monotherapy: 1 mg orally once daily Adjunct to levodopa with or without other Parkinson disease drugs: 0.5 mg orally once daily	50 mg orally once daily without regard to meals	5 mg orally twice daily
Dosage adjustment	Adjunct to levodopa with or without other Parkinson disease drugs: Increase to 1 mg once daily if insufficient clinical response	Increase to 100 mg once daily after at least 2 weeks	None
Maximum dose	1 mg daily	100 mg daily	10 mg/d
Mild hepatic impairment (Child-Pugh class A)	Maximum dose: 0.5 mg once daily		
Moderate hepatic impairment (Child-Pugh class B)	Avoid	Maximum dose: 50 mg orally once daily	
Severe hepatic impairment (Child-Pugh class C)	Avoid	Contraindicated	
Concomitant use of ciprofloxacin	Maximum dose: 0.5 mg once daily		

Conclusion

Safinamide is approved as adjunctive treatment to carbidopa/levodopa in patients with Parkinson disease experiencing “off” episodes. Safinamide’s long half-life and high bioavailability allow for once-daily dosing with or without food. While safinamide showed evidence of short-term efficacy, long-term study results indicate that the therapeutic benefit of safinamide may diminish over time. This phenomenon is observed with most medications available for Parkinson disease, likely due to the progressive nature of the disease. Safinamide is well tolerated; long-term safety data indicate that it is safe to use, for at least 2 years. There are currently no head-to-head trials comparing safinamide with other selective MAO-B inhibitors.

Declaration of Conflicting Interests

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