

Brand Name: Xadago

Generic Name: Safinamide

Manufacturer¹: Newron Pharmaceuticals

Drug Class^{1,2,4}: Anti-Parkinson agent; Monoamine Oxidase Type B Inhibitor

Uses:

Labeled Uses^{2,3,4,5}: Adjunctive treatment to levodopa-carbidopa therapy in patients with Parkinson's disease experiencing *off* episodes

Unlabeled Uses: None

Mechanism of Action^{1,3}:

The exact mechanism in treating *off* episodes is unknown; however, it's estimated that safinamide has at least a 1000-fold greater selectivity for monoamine oxidase B (MAO-B) over monoamine oxidase A (MAO-A). Studies suggest that inhibition of MAO-B further blocks the catabolism of dopamine. Consequently, this results in an increase in dopamine levels and dopaminergic activity in the brain.

Pharmacokinetics:

Absorption^{1,2}:

T _{max}	2-3 hours
V _d	165 L
t _{1/2}	20-26 hours
Clearance	4.6 L/hr
Protein Binding	88-89%
Bioavailability	95%

Metabolism^{1,2}: Metabolism occurs primarily through the liver. Amidases in the liver undergo hydrolytic oxidation, oxidative cleavage, and glucuronidation to convert safinamide into its inactive metabolites: safinamide acid, O-debenzylated safinamide, and N-dealkylated acid. N-dealkylated acid is the main circulating metabolite in human plasma. CYP3A4 and other CYP iso-enzymes also play a minor role in the metabolism of safinamide.

Elimination²: Elimination occurs primarily through the kidneys with 76% as inactive metabolites and approximately 5% as unchanged safinamide.

Efficacy^{6,7,8}:

Stocchi F, Borgohain R, Onofri M, Schapira A, Bhatt M, Lucini V, et al. A randomized, double-blind, placebo-controlled trial of safinamide as add-on therapy in early Parkinson's disease patients. *Mov Disord.* 2012;27(1):106-12.

Study Design: Phase III, randomized, double-blind, placebo-controlled, parallel-group, clinical trial

Description of Study:

Methods: A total of 270 patients with a clinical diagnosis of idiopathic Parkinson's Disease and

duration of less than 5 years were randomized to receive safinamide 200 mg/day, 100 mg/day, or placebo. Participants were required to be on a stable dose of a single dopamine agonist for at least 4 weeks prior to screening. After a 10-day screening and run-in period, participants were started on a low dose of safinamide (100 mg or 50 mg respectively). After 2 weeks, patients were increased to the target dose. The primary efficacy measure was the change in Unified Parkinson's Disease Rating Scale (UPDRS) part III (motor examination) total score from baseline. Secondary measures included percent of responders.

Outcomes/Results: 37 patients failed to complete the study: 19 in the 200 mg/day group, 9 in the 100 mg/day group, and 9 in the placebo group. When analyzing the primary outcome, change in UPDRS part III scores, the 200 mg/day group experienced a mean change of -0.4 points (CI: -2.3 to 1.4; $p = 0.65$, when compared to placebo), and the 100 mg/day group experienced a mean change of -1.9 points (CI: -3.7 to -0.1; $p = 0.04$, when compared to placebo). The most common adverse effects were nausea, headache, abdominal pain, vomiting, pyrexia, and cough. The proportion of patients with severe adverse effects was significantly higher in the 200 mg/day group (10.1%) in comparison to the 100 mg/day group (2.2%) and placebo (6.7%). The proportion of patients who were responders was higher in the treatment groups than placebo.

Limitations: The partnership of U.S. WorldMeds and Zambon was established to aid Newron Pharmaceuticals in the manufacturing of safinamide. The company oversaw many parts of the study design including investigator selection, research organization selection, data management, etc. This is a potential conflict of interest, especially given some of the authors' affiliations with Newron. It's unknown whether similar protocol was followed at each site given the international scope. The high incidence of discontinuations in the 200 mg/day group could potentially have altered the ability to determine a clinical benefit from the study in that group. The study also did not account for or control for medications (other than dopamine agonists) that could've potentially altered the results.

Conclusion: The results of the study demonstrated that the addition of 100 mg/day of safinamide to a stable dose of a dopamine agonist can improve motor symptoms in patients with early Parkinson's disease. Further studies are needed to truly determine whether the effect is dose-dependent and why the 200 mg/day group did not demonstrate a significant improvement, if so. Also, more studies would be beneficial to determine the effects of this drug on later-stage Parkinson's patients.

Borghain R, Szasz J, Stanzione P, Chandreashekar M, Bhatt M, Chirilineau D, et al. Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. *Mov Disord.* 2014;29(10):1273-80.

Study Design: Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study

Description of Study:

Methods: A total of 669 patients with mid-to-late stage Parkinson's Disease (≥ 3 years) and motor fluctuations were randomized to receive either safinamide 100 mg/day, 50 mg/day, or placebo daily in addition to current levodopa and other dopaminergic treatments. The study took place in 52 centers in India, Romania, and Italy. Patients with evidence of dementia, major psychiatric illnesses, and/or severe and progressive medical illnesses were excluded. Concomitant treatments with dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors, amantadine, and/or anticholinergics was permitted. Safety assessments were done regularly for change in vitals,

laboratory data, and treatment-emergent adverse events. The primary efficacy variable was the change in mean daily total *on* time with no or nontroublesome dyskinesia per patient diaries. Secondary efficacy variables included: total daily *off* time, UPDRS Part III (motor) scores, CGI-C scores.

Outcomes/Results: At week 24, mean \pm SD increases in total *on* time with no or nontroublesome dyskinesia were 1.36 ± 2.625 hours daily for safinamide 100 mg/day (0.55 hours; 95% CI, 0.12-0.99, $p = 0.013$), 1.37 ± 2.745 hours for safinamide 50 mg/day (0.51 hours; 95% CI, 0.07-0.94, $p = 0.022$), and 0.97 ± 2.375 hours for placebo. There was a statistically significant improvement in patients with mid-to-late Parkinson's disease and motor symptoms in duration of *on* time while taking safinamide. Improvements in *off* time, UPDRS Part III, and CGI-C were significantly greater in both safinamide groups vs. placebo. There was no increase in troublesome dyskinesia during the treatment period despite the increased incidence of mild-moderate dyskinesia. There were no significant differences between groups for incidence of treatment-emergent adverse events. The most common adverse effects were dyskinesia, cataracts, back pain, depression, headache, and hypertension. A total of 594 patients completed the trial with 75 lost to follow up.

Limitations: At baseline, 80% of the population was from India. This makes the results fairly ungeneralizable to other races and populations. Much of the study results were based on diary entries. Requiring patients with motor dysfunction to write diary entries every 30 minutes for 18 hours a day can be severely troublesome. The method of determining compliance was simply based on whether the entries were filled out, not whether they were filled out at the appropriate time periods. Also, some of the authors had affiliations and/or were employed with Newron Pharmaceuticals, the manufacturer of safinamide. Funding was provided, as well, from Newron Pharmaceuticals, which is a potential conflict of interest in the study.

Conclusion: The study states that the benefits of safinamide were more often observed with the 100 mg/day dose; however the actual difference from placebo between the 100 mg/day dose and the 50 mg/day dose was nonsignificant. With this information, the effects of safinamide do not appear to be dose-dependent. It's debatable whether the increase of *on* time would be clinically significant at approximately half an hour per day when compared to placebo. The large sample size, high power, and appropriate level of significance make it reasonable to accept the idea that, in patients with mid-to-late Parkinson's disease with motor dysfunction, taking safinamide at a dose of 50 mg/day or 100 mg/day in addition to levodopa mildly increases the incidence of *on* time with no increased incidence in adverse events. Further studies would be beneficial in order to continue to evaluate the dose-response curve and long-term efficacy and safety of safinamide in this patient population and to explore other populations geographically.

Schapira A, Fox S, Hauser R, Jankovic J, Jost W, Kenney C, et al. Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson disease and motor fluctuations: a randomized clinical trial. JAMA Neurol. 2017;74(2):216-224.

Study Design: Phase III, randomized, double-blind, parallel-group, international clinical trial.

Description of Study:

Methods: A total of 549 levodopa-responsive patients with mid-to-late Parkinson's disease (≥ 3 years) were randomized to receive either safinamide at a dose of 50-100 mg per day or placebo once daily. Locations included 126 centers in Europe, the Asia-Pacific region, and North America. Participants were permitted to continue dopamine agonists, anticholinergic medications, COMT inhibitors, and/or amantadine at stable doses. Patients in the treatment group were

initiated on 50 mg/day. If there were no tolerability issues at day 14, they were increased to 100 mg/day. The treatment period continued for 24 weeks with an additional 1-week period for optional tapering. The primary outcome measured was change in mean daily *on* time from baseline as recorded by patients or caregivers in a diary maintained. Secondary outcomes included improvement in total daily *off* time, change in UPDRS Part III (motor examination) and Part II (activities of daily living) scores, improvement in CGI-C rating, and mean change in Parkinson Disease Questionnaire (PDQ-39) summary index scores. Safety was also measured in incidence of treatment-emergent adverse events.

Outcomes/Results: The mean increase in daily on time without troublesome dyskinesia was 1.42 ± 2.80 hours in the treatment group compared to 0.57 ± 2.47 hours in the placebo group. When adjusted for covariates, the least-squares mean difference was estimated to be 0.96 hour (95% CI, 0.56 to 1.37 hours; $p < 0.001$). Among secondary outcomes, the mean daily *off* time was 1.03 hours lower in the treatment group. Mean change in UPDRS Part III scores was 1.82 points lower in the treatment group. Mean change in UPDRS Part II scores was nonsignificant. The proportion of patients with improvement on the CGI-C scale was 57.7% vs 41.8%. Mean change in PDQ-39 scores was 2.33 points lower in the treatment group. Overall, more adverse effects were reported in the placebo group (69.1% vs 67.9%). The most common adverse effects were dyskinesia, fall, urinary tract infection, nausea, and headache. The incidence of dyskinesia was significantly greater in the treatment group at 14.6% vs 5.5%. 89.4% of patients in the treatment group and 87.6% of patients in the control group completed the study. Most discontinuations were due to withdrawal of consent rather than treatment-emergent adverse events.

Limitations: Many of the authors/researchers had affiliations with one or both of the companies which partnered to aid Newron Pharmaceuticals, the manufacturer of safinamide. Funding was provided by Newron. In various tables, the authors utilize standard error rather than standard deviation to minimize the visual representation of the variability. The method for determining compliance is not disclosed. Also, the diaries may be fairly inaccurate given the challenge of the patients and caregivers to accurately record an entry every 30 minutes.

Conclusion: The study provided a generalizable set of results that can be applied to a global population. It can be reasonably concluded that the addition of safinamide to patients with mid-to-late stage Parkinson's disease with motor symptoms is a relatively safe and effective option for increasing duration of *on* time in levodopa-stable patients at this time. Further studies would be useful to help eliminate the potential for bias due to the large influence of Newron Pharmaceuticals in this study; however no specific areas of bias are directly evident in the trial.

Contraindications^{1,2,3,4,5}:

Concomitant use of: other monoamine oxidase inhibitors, opioid drugs, selective norepinephrine reuptake inhibitors, tri-, tetra-cyclic or triazolopyridine antidepressants, cyclobenzaprine, methylphenidate, amphetamine, and their derivatives, St. John's wort, and dextromethorphan
A history of hypersensitivity to safinamide
Severe hepatic impairment (Child-Pugh C: 10-15)

Precautions^{1,2,3,4,5}:

Hypertension: Monoamine oxidase inhibitors can cause increased blood pressure in some patients. Monitor patients for new-onset hypertension or hypertension that is not adequately controlled after initiation of safinamide or after a recent dose increase. Use caution when being used concomitantly with sympathomimetic medications.

Serotonin Syndrome: Monoamine oxidase inhibitors are associated with an increased incidence of serotonin syndrome, especially when used in combination with selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, tetracyclic antidepressants, triazolopyridine antidepressants, cyclobenzaprime, opioid drugs, stimulants, and their derivatives. Always use the lowest effective dose for each patient. Symptoms include mental status changes, autonomic instability, neuromuscular symptoms, seizures, and/or gastrointestinal symptoms.

Falling Asleep during Activities of Daily Living: Dopaminergic medications tend to increase risk for falling asleep while engaging in daily activities such as driving. Some patients may not notice warning signs prior to the event. If this should occur, discontinue safinamide or instruct the patient to avoid potentially dangerous activities.

Dyskinesia: Safinamide could potentially exacerbate pre-existing dyskinesia or cause new-onset dyskinesia. In these patients, reducing the patient's daily dose of levodopa or another dopaminergic drug may help to resolve the dyskinesia.

Hallucinations/Psychosis: Patients with Parkinson's disease should generally not be treated with safinamide due to the potential to exacerbate the psychosis by increasing dopaminergic activity. Consider discontinuation or dosage reduction if a patient develops hallucinations or psychotic behaviors while taking safinamide.

Impulse Control: Desire to engage in compulsive behaviors such as gambling, sexual activities, binge eating, etc. may be increased while taking dopaminergic medications such as safinamide. Some patients may not recognize these behaviors as abnormal. It is important to screen for altered behaviors and consider a dosage reduction or discontinuation if evident.

Withdrawal-Emergent Hyperpyrexia and Confusion: Rapid dose reduction, withdrawal of, or changes in dopaminergic drugs may lead to a symptom complex similar to neuroleptic malignant syndrome. Be cautious of elevated temperature, muscular rigidity, altered consciousness, and autonomic instability when working with patients taking safinamide.

Retinal Pathology/Alteration: Loss of photoreceptor cells and retinal degeneration has occurred in rodent trials. Monitor patients for visual changes; especially when accompanied by a past medical history of retinal conditions or family history of altered retinal function.

Adverse Effects^{1,2,3}:

Occurring in >10% of patients:

Neurologic

Dyskinesia (17% to 21%)

Occurring in >1% to <10% of patients:

Cardiovascular

Hypertension (5% to 7%)

Orthostatic hypotension (2%)

Gastrointestinal

Indigestion (\leq 2%)

Nausea (3% to 6%)

Neurologic

Insomnia (1% to 4%)

Sleep, sudden onset (unknown)

Psychiatric Effects

Anxiety (2%)

Hallucinations (unknown)

Impulse control disorder (unknown)

Respiratory

Cough (2%)

Miscellaneous

Withdrawal-emergent hyperpyrexia and confusion

Falls (4% to 6%)

Serotonin Syndrome

Drug Interactions^{1,2,3}:

Monoamine Oxidase Inhibitors

Co-administration with medications which inhibit monoamine oxidase can increase risk for hypertensive crises. At least 14 days should elapse between discontinuation of safinamide and initiation of treatment with other MAOIs.

Isocarboxazid, moclobemide, phenelzine, tranylcypromine, pirazidol, selegiline, toloxatone, hydracarbazine, isoniazid, linezolid, procarbazine, rasagiline

Opioid Drugs

Serious, sometimes fatal, reactions have occurred with the combined use of opioid medications and MAO inhibitors. Concomitant use is contraindicated.

Morphine sulfate, buprenorphine, methadone, fentanyl, hydromorphone, tapentadol, oxycodone, hydrocodone, oxycodone, tramadol, propoxyphene, and meperidine and its derivatives

Serotonergic Drugs

Concomitant use of safinamide with SNRI's, and other serotonergic medications, increases risk for serotonin syndrome. Although not contraindicated, extreme caution should be used with patients taking SSRI's in combination with safinamide.

Venlafaxine, desvenlafaxine, milnacipran, duloxetine, levomilnacipran, triazolopyridine, cyclobenzaprine, St. John's wort, amoxapine, desipramine, doxepin, clomipramine, trimipramine, amitriptyline, imipramine, nortriptyline, protriptyline, maprotiline, mirtazapine, fluoxetine, fluvoxamine, escitalopram, paroxetine, citalopram, sertraline

Dextromethorphan

Concomitant use of MAO inhibitors and dextromethorphan has been linked to episodes of psychosis or bizarre behavior.

Sympathomimetics

The use of MAO inhibitors in combination with sympathomimetic medications has been linked to severe hypertensive reactions. Monitor patients for hypertension if safinamide is prescribed concomitantly with prescription or nonprescription sympathomimetic medications.

Norepinephrine, isoproterenol, amphetamine, methylphenidate, phenylpropanolamine, epinephrine, apraclonidine, dipivefrine hydrochloride, brimonidine tartrate, phenylephrine, pseudoephedrine, naphazoline, tetrahydrozoline

Tyramine

The presence of MAO in the gastrointestinal tract and liver provide protection from exogenous

amines such as tyramine. Increased tyramine could lead to severe hypertension. Patients should avoid foods containing a large amount of tyramine while taking safinamide.

Substrates of Breast Cancer Resistance Protein (BCRP)

Safinamide and its major metabolite could potentially inhibit intestinal BCRP which could increase plasma concentrations of BCRP substrates. Monitor for increased pharmacologic or adverse effects of BCRP substrates if used in combination with safinamide.

Methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan

Dopaminergic Antagonists

Medications that antagonize dopamine can potentially decrease the effectiveness of safinamide and worsen Parkinson's symptoms.

Acepromazine, asenapine, clomipramine, chlorpromazine, fluphenazine, haloperidol, hydroxyzine, metoclopramide, olanzapine, paliperidone, perphenazine, prochlorperazine, quetiapine, risperidone, thioridazine, trifluoperazine, ziprasidone

Dosing/Administration^{1,3,4}:

Adult Dosing

50 mg orally once daily at the same time; may increase to 100 mg daily after 2 weeks

Pediatric Use

Safety and efficacy in this population has not been studied.

Geriatric Use

No significant differences in safety or efficacy have been observed in geriatric patients; however, greater sensitivity of some older individuals cannot be ruled out at this time.

Renal Impairment

No dose adjustment is necessary

Hepatic Impairment

Plasma concentrations of safinamide are increased in patients with hepatic impairment. In moderate hepatic impairment (Child-Pugh B: 7-9), the maximum recommended dose of safinamide is 50 mg once daily. Safety and efficacy in severe hepatic impairment (Child Pugh C: 10-15) has yet to be determined. If patients develop severe hepatic impairment, safinamide should be discontinued.

Pregnancy

Safinamide has not been studied in pregnant patients. In animal studies, teratogenic effects were observed at clinically relevant doses. Safinamide should be used in pregnancy only if the benefit outweighs the potential teratogenic risks to the fetus.

Nursing Mothers

Skin discoloration due to hyperbilirubinemia resulting from hepatobiliary toxicity has been observed in animal studies after indirect exposure to safinamide through lactation. It's unknown whether this medication is present in human milk. Due to the lack of studies and the potential for serious adverse reactions in nursing infants, one should weigh the benefits with the risks when deciding whether to continue this medication

Use in Special Circumstances^{1,2,3}:

Overdose: There is no current experience with safinamide overdose. There is no known antidote for safinamide nor any specific treatment currently outlined for overdose. If overdose occurs, treatment should be discontinued and supportive treatment should be administered as indicated. Dietary tyramine restriction should be observed for several weeks. The Poison Control Center should be contacted at 1-800-222-1222 for the most current guidelines.

Conclusion:

Safinamide is an effective adjunct therapy for patients with Parkinson's disease and motor fluctuations. Safinamide appears to exhibit a minimal amount of side effects, with the main risk being potential for increased incidence of mild dyskinesia. This is common with all dopaminergic agents. It has shown efficacy in improvement of motor symptoms as well as increased daily duration of *on* time when used in combination with levodopa. Further studies are needed to determine if similar evidence is seen when used as a monotherapy. Further studies would also be useful to compare safinamide with current MAO inhibitors used to treat Parkinson's symptoms in order to determine the clinical role of this medication in practice. Pricing information is currently unavailable and may play a role in selection of medications in this population. With its tolerability, minimal drug interactions, and effectiveness at decreasing Parkinson's symptoms, safinamide appears to be an additional, clinically-useful adjunct for Parkinson's treatment.

Recommended References:

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8. Schapira A, Fox S, Hauser R, Jankovic J, Jost W, Kenney C, et al. Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson disease and motor fluctuations: a randomized clinical trial. *JAMA Neurol.* 2017;74(2):216-224.

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