

INTRODUCTION

- Parkinson's disease (PD) is a neurodegenerative disorder caused by progressive dopamine depletion in the nigrostriatal pathway of the brain and characterized by the cardinal manifestations of tremor, bradykinesia, and rigidity. Although traditionally recognized as a motor disorder, PD is a complex multifactorial condition that also includes neuropsychiatric and other nonmotor manifestations. The disease is diagnosed in an estimated 50,000 people each year in the United States, with about half a million people living with the disease (*Chou 2017, Jankovic 2017, National Institute of Health [NIH] 2010*).
- The dopamine precursor levodopa is the most effective drug for the symptomatic treatment of PD and the preferred choice as symptoms, especially bradykinesia, become troublesome; however, levodopa-induced complications (eg, motor fluctuations ["wearing off" phenomenon], dyskinesia, dystonia) develop within several years of starting levodopa in a substantial number of patients (*Tarsy 2017b*).
 - Levodopa complications may be managed through levodopa dose adjustments or the addition of a dopamine agonist (DA), a catechol-O-methyl transferase (COMT) inhibitor, or a monoamine oxidase (MAO)-B inhibitor (*Tarsy 2017a*).
- There are currently 3 unique MAO-B inhibitors that are Food and Drug Administration (FDA)-approved for use in PD. Selegiline was FDA-approved in 1989 and is indicated as an adjunct in the management of patients with PD being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy. It carries the limitation that there is no evidence from controlled studies that selegiline has any beneficial effect in the absence of concurrent levodopa therapy. An additional selegiline orally-disintegrating tablet (ODT) shares the same indication. Rasagiline was FDA-approved in 2006 and is indicated for the treatment of PD as monotherapy, as an adjunct without levodopa, or as an adjunct to levodopa. The newest molecular entity, safinamide, was FDA-approved in March 2017 as adjunctive treatment to levodopa/carbidopa in patients with PD experiencing "off" episodes with the limitation that it has not been shown to be effective as monotherapy for the treatment of PD (*FDA Web site*).
- Safinamide is an α -aminoamide with both dopaminergic and nondopaminergic actions, including inhibition of MAO-B, sodium channel blockage, and modulation of stimulated release of glutamate. The clinical implications of its actions beyond MAO-B inhibition are currently unclear (*Borgohain et al 2014a*).
- Medispans class: Antiparkinson Agents; Antiparkinson Monoamine Oxidase Inhibitors

INDICATIONS

- Safinamide is indicated as adjunctive treatment to levodopa/carbidopa in patients with PD experiencing "off" episodes (*Xadago prescribing information 2017*).
Limitations of Use: Safinamide has not been shown to be effective as monotherapy for the treatment of PD.
- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The safety and efficacy of safinamide as levodopa add-on therapy was demonstrated in two 24-week, double-blind (DB), placebo-controlled (PC), randomized controlled trials (RCTs) and an 18-month extension study. Patients with mid-to-late stage PD experiencing motor fluctuations while receiving levodopa and other dopaminergic treatments were randomized to receive safinamide or placebo in combination with their baseline treatment regimen. Study 016 examined both safinamide 50 mg and safinamide 100 mg once daily, while the SETTLE study initiated patients at safinamide 50 mg and titrated to a target dose of 100 mg. The primary efficacy endpoint in both Study 016 and SETTLE was change in mean daily total "on" time with no or nontroublesome dyskinesia from baseline as recorded in patient diaries. Patients treated with safinamide had a statistically significant increase in "on" time in both studies (see Table 1). Treatment-emergent adverse event (TEAE) rates were similar between safinamide and placebo groups, although dyskinesia was reported more frequently in safinamide-treated patients (*Borgohain et al 2014a, Schapira et al 2017*).
 - The 18-month extension study (Study 018) enrolled patients from Study 016 and maintained blinding. The primary endpoint was mean change from baseline (at Study 016 start) to study completion of the total score of the Dyskinesia

Rating Scale (DRS) during “on” time. There were no statistically significant changes in DRS score in the safinamide groups vs. placebo, but the authors attributed this to the low average DRS scores at baseline. The secondary endpoint of mean “on” time without troublesome dyskinesia showed a continued trend as demonstrated in the original 24-week Study 016 (see Table 1) (*Borghain et al 2014b*).

Table 1. Mean daily total “on” time with no or nontroublesome dyskinesia

	Baseline* (hr)	Δ from baseline* (hr)	LS difference vs. placebo (95% CI)	p-value vs. placebo
Study 016				
Placebo (n = 222)	9.3	0.8	--	--
Safinamide 50 mg (n = 223)	9.4	1.23	0.51 (0.07 to 0.94)	0.0223
Safinamide 100 mg (n = 224)	9.6	1.28	0.55 (0.12 to 0.99)	0.0130
SETTLE				
Placebo (n = 275)	9.06	0.57	--	--
Safinamide 100 mg (n = 274)	9.30	1.42	0.96 (0.56 to 1.37)	< 0.001
Study 018 18-month extension**				
Placebo (n = 222)	9.301	0.34	--	--
Safinamide 50 mg (n = 223)	9.373	1.01	0.67 (0.23 to 1.11)	0.0031
Safinamide 100 mg (n = 224)	9.520	1.18	0.83 (0.39 to 1.27)	0.0002

Abbreviations: CI = confidence interval, LS = least squares, Δ = change

* Least squares mean

** Mean daily total “on” time with no or nontroublesome dyskinesia was evaluated as a secondary endpoint; intention-to-treat (ITT) population from Study 016 used

- Safinamide has been studied in patients with early PD on DA therapy without motor fluctuations; however, the studies failed to show statistical superiority of safinamide over placebo in the primary efficacy endpoint of improvement in the Unified Parkinson’s Disease Rating Scale (UPDRS) Part III (motor) scores from baseline to end of study. Therefore, safinamide was not given an indication for use in early PD (*FDA Medical Review 2017, Stocchi et al 2012*).

CLINICAL GUIDELINES

- Current PD guidelines from the American Academy of Neurology (AAN), the European Federation of Neurological Societies (EFNS) and the Movement Disorders Society (MDS) recommend the addition of either a COMT inhibitor or MAO-B inhibitor to therapy in patients experiencing levodopa-induced motor fluctuations; no recommendations can be made as to which treatment should be chosen first. On average, both classes of medication reduce daily “off” time by 1 to 1.5 hours. The guidelines have not yet been updated to address safinamide (*Fox et al 2011, Oertel 2011, Pahwa et al 2006*).

SAFETY SUMMARY

- **Contraindications:**
 - Concomitant use of the following drugs:
 - Other MAO inhibitors or other drugs that are potent inhibitors of MAO (eg, linezolid)
 - Opioid drugs (eg, tramadol, meperidine and related derivatives)
 - Selective norepinephrine reuptake inhibitors (SNRIs)
 - Tri- or tetra-cyclic or triazolopyridine antidepressants (TCAs)
 - Cyclobenzaprine
 - Methylphenidate, amphetamine, and their derivatives
 - St. John’s wort
 - Dextromethorphan
 - Severe hepatic impairment (Child-Pugh C)
- **Warnings and Precautions:**
 - May cause or exacerbate hypertension
 - May cause serotonin syndrome when used with MAO inhibitors, antidepressants, or opioid drugs
 - May cause falling asleep during activities of daily living
 - May cause or exacerbate dyskinesia; levodopa dose reduction should be considered

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- May cause hallucinations and psychotic behavior
- May cause problems with impulse control/compulsive behaviors
- May cause withdrawal-emergent hyperpyrexia and confusion
- **Adverse Events (AEs):**
 - The most common AEs (incidence on safinamide 100 mg/day at least 2% greater than placebo) were dyskinesia, fall, nausea, and insomnia.

DOSING AND ADMINISTRATION

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Xadago (safinamide)	50 mg, 100 mg tablets	Oral	50 mg daily for 2 weeks, then increased to 100 mg daily based on individual need and tolerability	Dose adjustment is necessary in moderate hepatic impairment (Child-Pugh B). Safinamide is contraindicated in severe hepatic impairment.

See the current prescribing information for full details

CONCLUSION

- Safinamide, a novel α -aminoamide with similar action to the MAO-B inhibitors rasagiline and selegiline, has demonstrated safety and efficacy as adjunct treatment to levodopa in patients with mid-to-late stage PD experiencing motor fluctuations.
 - Safinamide, unlike rasagiline, is not indicated for use as monotherapy and has not demonstrated clinical efficacy in patients with early PD.
- Contraindications of safinamide include concomitant use of opioids, SNRIs, TCAs, amphetamines, and dextromethorphan, as well as severe hepatic impairment; safinamide may cause or exacerbate hypertension, somnolence, hallucinations, compulsive behavior, and dyskinesias. The most common AEs experienced by safinamide-treated patients were dyskinesia, fall, nausea, and insomnia.
- Current guidelines recommend a COMT inhibitor or MAO-B inhibitor as adjunct therapy in patients experiencing levodopa-induced motor fluctuations; no recommendations can be made as to which treatment should be chosen first. The guidelines have not been updated to include safinamide (*Fox et al 2011, Oertel 2011, Pahwa et al 2006*).

REFERENCES

- Borgohain R, Szasz J, Stanzione P, et al. Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. *Mov Disord.* 2014a;29(2):229-37.
- Borgohain R, Szasz J, Stanzione P, et al. Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease. *Mov Disord.* 2014b;29(10):1273-80.
- Cattaneo C, Sardina M, Bonizzoni E. Safinamide as add-on therapy to levodopa in mid- to late-stage Parkinson's disease fluctuation patients: post hoc analyses of Studies 016 and SETTLE. *J Parkinsons Dis.* 2016;6(1):165-73.
- Chou KL. Clinical manifestations of Parkinson disease. UpToDate Web site. Updated July 17, 2017. www.uptodate.com. Accessed August 11, 2017.
- Food and Drug Administration. Xadago medical review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/207145Orig1s000MedR.pdf. March 21, 2017. Accessed August 11, 2017.
- Food and Drug Administration/Center for Drug Evaluation and Research. FDA approved drug products. FDA Web site. <https://www.accessdata.fda.gov/scripts/cder/daf/>. Accessed August 11, 2017.
- Fox SH, Katzenschlager R, Lim SY, et al. The Movement Disorder Society evidence-based medicine review update: treatments for the motor symptoms of Parkinson's Disease. *Mov Disord.* 2011;26 Suppl 3:S2-41.
- Jankovic J. Etiology and pathogenesis of Parkinson disease. UpToDate Web site. Updated July 17, 2017. www.uptodate.com. Accessed August 11, 2017.
- National Institute of Health (NIH). Parkinson's disease fact sheet. NIH Web site. Updated October 2010. [https://report.nih.gov/NIHfactsheets/Pdfs/ParkinsonsDisease\(NINDS\).pdf](https://report.nih.gov/NIHfactsheets/Pdfs/ParkinsonsDisease(NINDS).pdf). Accessed August 11, 2017.
- Oertel WH, Berardelli A, Bloem BR, et al. Late (complicated) Parkinson's disease. In: Gilhus NE, Barnes MP, Brainin M, eds. *European Handbook of Neurological Management*. West Sussex, United Kingdom: Wiley-Blackwell; 2011:237-267.
- Pahwa R, Factor SA, Lyons KE, et al. Practice Parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the quality standards subcommittee of the American Academy of Neurology. *Neurology.* 2006;66:983-95.
- Schapira AH, Fox SH, Hauser RA, et al. Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson disease and motor fluctuations. *JAMA Neurol.* 2017;74(2):216-24.

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- Stocchi F, Borgohain R, Onofrij M, 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.
- Tarsy D. Motor fluctuations and dyskinesia in Parkinson disease. UpToDate Web site. Updated March 23, 2017a. www.uptodate.com. Accessed August 11, 2017.
- Tarsy D. Neuroprotective therapy for Parkinson disease. UpToDate Web site. Updated October 13, 2016. www.uptodate.com. Accessed August 11, 2017.
- Tarsy D. Pharmacologic treatment of Parkinson disease. UpToDate Web site. Updated August 3, 2017b. www.uptodate.com. Accessed August 11, 2017.
- Xadago [package insert], Louisville, KY: US WorldMeds, LLC; May 2017.

Publication Date: September 13, 2017