Clinical Policy Title:	safinamide
Policy Number:	RxA.303
Drug(s) Applied:	Xadago®
Original Policy Date:	02/07/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

Safinamide (Xadago®) is monoamine oxidase type B (MAO-B) inhibitor. Safinamide is indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
safinamide (Xadago®)	Adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes.	50 mg orally once daily; 100 mg orally once daily after 2 weeks if needed. Hepatic Impairment (Child Pugh B 7-9): Do not exceed 50 mg once daily in patients with moderate hepatic impairment; contraindicated in patients with severe hepatic impairment (Child Pugh C:10-15).	100 mg once daily.

Dosage Forms

- Tablets: 50 mg and 100 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Parkinson's Disease (must meet all)**:**

1. Diagnosis of idiopathic Parkinson's disease (PD);
2. Age ≥ 18 years;
3. Prescribed by or in consultation with neurologist;

4. Member is experiencing "off" time (see Appendix B) on levodopa/carbidopa therapy;
5. Failure of two drugs, as specified below, unless contraindicated or clinically significant adverse effects are experienced (a and b):
   a. Rasagiline;
   b. One of the following drugs: entacapone (Comtan®/Stalevo®), ropinirole/ropinirole ER,pramipexole/pramipexole ER, Neupro®;
   *Prior authorization may be required for the above agents
6. Xadago® is prescribed in combination with levodopa/carbidopa;
7. Dose does not exceed 100 mg per day.

Approval duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Parkinson's Disease (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. Dose does not exceed 100 mg per day.

Approval duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A*:* Abbreviation/Acronym Key
COMT: Catechol-O-methyl transferase
MAO B: Monoamine oxidase inhibitor
FDA: Food and Drug Administration
PD: Parkinson's disease
ER: Extended- release

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/Maximum Dose
COMT Inhibitors		
entacapone (Comtan®)	Oral: 200 mg with each dose of levodopa/carbidopa.	1600 mg daily (divided doses)
carbadopa/levodopa/ entacapone (Stalevo®)	Oral: Dose should be individualized based on therapeutic response; doses may be adjusted by changing strength or adjusting interval. Fractionated doses are not recommended and only 1 tablet should be given at each dosing interval.	300 mg/day orally carbidopa; 1,200 mg/day orally levodopa; 1,600 mg/day orally of entacapone.
MAO B Inhibitors		

Drug Name	Dosing Regimen	Dose Limit/Maximum Dose
rasagiline (Azilect®)	Oral: Monotherapy or adjunctive therapy (not including levodopa): 1 mg once daily. Adjunctive therapy with levodopa: Initial: 0.5 mg once daily; may increase to 1 mg once daily based on response and tolerability.	1 mg/day once daily.
Dopamine agonists		
ropinirole IR	Oral: Recommended starting dose: 0.25 mg 3 times/day. Based on individual patient response, the dosage should be titrated with weekly increments: Week 1: 0.25 mg 3 times/day; total daily dose: 0.75 mg; week 2: 0.5 mg 3 times/day; total daily dose: 1.5 mg; week 3: 0.75 mg 3 times/day; total daily dose: 2.25 mg; week 4: 1 mg 3 times/day; total daily dose: 3 mg. After week 4, if necessary, daily dosage may be increased by 1.5 mg/day on a weekly basis up to a dose of 9 mg/day, and then by up to 3 mg/day weekly to a total of 24 mg/day.	24 mg/day orally (divided doses).
Ropinirole ER	Oral: Initial dose: 2 mg once daily for 1 to 2 weeks, followed by increases of 2 mg/day at weekly or longer intervals based on therapeutic response and tolerability.	24 mg once daily.
pramipexole (Mirapex®)	Oral: Initial dose: 0.125 mg 3 times daily, increase gradually every 5 to 7 days; maintenance (usual): 0.5 to 1.5 mg 3 times daily.	4.5 mg daily (divided doses).
pramipexole (Mirapex ER®)	Oral: Initial dose: 0.375 mg once daily; increase gradually not more frequently than every 5 to 7 days to 0.75 mg once daily and then, if necessary, by 0.75 mg per dose.	4.5 mg once daily.
Neupro®	Transdermal: Initial dose: 2 mg/24 hours for early-stage disease or 4 mg/24 hours for advanced-stage disease.	6 mg/24 hours for early-stage disease; 8 mg/24 hours for advanced-stage disease.

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand, Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

APPENDIX C: Contraindication/Boxed Warnings

- Contraindication(s):
  - Concomitant use with MAOI class or other drugs that are potent inhibitors of monoamine oxidase (e.g., linezolid);

- Concomitant use of opioids (e.g., tramadol, meperidine and related derivatives) serotonin-norepinephrine reuptake inhibitors; tri-or tetra-cyclic or triazolopyridine antidepressants or triazolopyridine antidepressants, cyclobenzaprine, methylphenidate or amphetamine and its derivatives, St.John's wart;
- Concomitant use with dextromethorphan;
- Severe hepatic impairment (Child-Pugh C: 10-15);
- A history of a hypersensitivity to safinamide.

- Boxed warning(s):
  - None Reported.

APPENDIX D: General Information

- PD symptoms, resulting from too little L-dopa, are in contrast with dyskinesia which typically results from too much L-dopa. The alterations between "on" time (the time when PD symptoms are successfully suppressed by L-dopa) and "off" time is known as "motor fluctuations".
- The addition of carbidopa to levodopa (L-dopa) prevents conversion of L-dopa to dopamine in the systemic circulation and liver.
- Off time/episodes represent a return of PD symptoms (bradykinesia, rest tremor or rigidity) when the L-dopa treatment effect wears off after each dosing interval.

References

1. Xadago Prescribing Information. Louisville, KY: US World Meds, LLC; November 2019. Available at: http://xadago.com/. Accessed July 12, 2021.
2. Pahwa MD, 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. April 2007; 66: 983-995. Available at: https://pubmed.ncbi.nlm.nih.gov/16606909/. Accessed July 12, 2021.
3. Borgohain R, Szasz J, Stanzione P, et al. Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. Movement Disorders. 2014; 29(2): 229-237. Available at: https://pubmed.ncbi.nlm.nih.gov/24323641/. Accessed July 12, 2021.
4. Schapira AHV, 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: A randomized clinical trial. JAMA Neurol. December 12, 2016. Available at: https://jamanetwork.com/journals/jamaneurology/fullarticle/2591318 . Accessed July 12, 2021.
5. Rinne UK, Larsen JP, Siden A, et al. Nomecomt Study Group. Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Neurology. November 1998; 51(5): 1309-14. Available at: https://pubmed.ncbi.nlm.nih.gov/9818851/. Accessed July 12, 2021.
6. Parkinson Study Group. Entacapone improves motor fluctuations in levodopa-treated parkinson's disease patients. Ann Neurol. 1997; 42: 747-755. Available at: https://pubmed.ncbi.nlm.nih.gov/9392574/. Accessed July 12, 2021.
7. Rascol O, Brooks DJ, Melamed E, et al. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. Lancet. 2005; 365: 947-54. Available at: https://pubmed.ncbi.nlm.nih.gov/15766996/. Accessed July 12, 2021.
8. Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa treated patients with Parkinson disease and motor fluctuations: The PRESTO study. Arch Neurol. 2205; 62: 241-248. Available at: https://pubmed.ncbi.nlm.nih.gov/15710852/ . Accessed July 12, 2021.
9. Poewe WH, Rascol O, Quinn N, et al. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: A double-blind, double dummy, randomized controlled trial. Lancet Neurol. June 2007; 6(6): 513-20. Available at: https://pubmed.ncbi.nlm.nih.gov/17509486/ . Accessed July 12, 2021.

10. Clinical Pharmacology [database online]. Available at: http://www.clinicalpharmacology-ip.com/ . Accessed July 12, 2021.
11. Xadago®. Micromedex Solutions. Truven Health Analytics Inc. Ann Arbor, MI. Available at: http://www.micromedexsolutions.com. Accessed July 12, 2021.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	1/2020	02/07/2020
Policy was reviewed: 3. **Statement about provider sample "The provision of provider samples does not guarantee coverage…" was added to Clinical Policy. Initial Approval criteria I.A.2 was updated to include age criteria, "** 6. **Continued Therapy Approval Criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...".** 7. **Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance..". Appendix B: Therapeutic Alternatives maximum dose for Stalevo was updated from "1200mg daily (divided doses)" to "**	7/12/2021	09/14/2021

9. **Appendix B: Therapeutic Alternatives was updated to remove discontinued drugs Requip and Requip XR and to remove inactive/unavailable drug rotigotine.** 10. **Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". References were reviewed and updated.**		