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Drug Class Update with New Drug Evaluation: Anti-Parkinson's Agents

Date of Review: March 2018
Generic Name: safinamide

End Date of Literature Search: 01/03/2018
Brand Name (Manufacturer): Xadago® (US WorldMeds)
Dossier Received: Yes

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
To evaluate for new comparative evidence between anti-Parkinson's agents and review the evidence and place in therapy of safinamide, which was recently approved by the United States (U.S.) Food and Drug Administration (FDA) as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes.

Research Questions:
1. Is there new comparative evidence that anti-Parkinson's agents differ in efficacy or effectiveness for alleviating symptoms and stabilizing disease in adults with PD?
2. Is there new comparative evidence that anti-Parkinson's agents differ in serious adverse events or tolerability when used to manage adults with PD?
3. Are there specific subpopulations (based on age, gender, race, disease severity, disease subtype, or concomitant therapies) for which one anti-Parkinson's agent is better tolerated or more effective than other available agents for PD?

Conclusions:
- One new guideline from the National Institute for Health and Care Excellence (NICE) was identified since the time of last review which supports the current preferred drug list (PDL) and prior authorization (PA) criteria.[1] One new FDA-approved formulation of extended-release amantadine (Gocovri™) which is indicated for treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy was identified since the time of last review.[2] No new safety alerts or comparative evidence of anti-Parkinson's agents were identified.
- There is low quality of evidence that amantadine ER improves dyskinesia as rated by the Unified Dyskinesia Rating Scale (UDysRS) with treatment differences compared to placebo of -7.9 points and -14.4 points (studies=2). UDysRS total scores range from 0 to 104 with higher scores indicating greater severity of dyskinesia.[3]
- There is low quality of evidence that adjunct safinamide 100 mg in addition to levodopa therapy improves total daily "on" time with no or non-troublesome dyskinesia compared to placebo at 24 weeks (Study-016: mean difference vs. placebo 0.55 hours per day (h/d); 95% CI 0.07-0.94; p=0.0223; SETTLE study:

mean difference vs. placebo 0.96 h/d; 95% CI 0.56 to 1.37; p<0.001) in patients with mid-late PD with moderate severity disease (mean Hoehn and Yahr score of 2.8 and 2.5 in the two trials, respectively).[4,5]

- There is low quality of evidence that adjunct safinamide 100 mg in addition to levodopa therapy improves total daily "off" time compared to placebo at 24 weeks (Study-016: mean difference vs. placebo -0.6 h/d; 95% CI -1.0 to -0.2; p=0.0034; SETTLE study: mean difference vs. placebo -1.03 h/d; 95% CI -1.40 to -0.67; p<0.001).[4,5]
- There is low quality of evidence that adjunct safinamide 100 mg in addition to levodopa therapy improves Parkinson's-disease health related quality of life as rated by the Parkinson's Disease Questionnaire (PDQ-39) scale compared to placebo at 24 weeks (Study-016: -28.4 vs. -11.9 points, respectively, on total PDQ-39 scale; mean difference -16.5 points; 95% CI -31.9 to -1.1; p=0.0360; SETTLE study: -3.17 and -0.68 points, respectively, on the PDQ-39 summary index; mean difference -2.49; 95% CI -3.98 to -0.68; p=0.006).[4,5] The maximum total score on the total PDQ-39 scale which indicates worst health-related quality of life is 800, while the maximum score on the PDQ-39 summary index is 100.[6,7] A minimum clinically important difference on the PDQ-39 summary index is considered by NICE guidance to be around 1.6 points.[6,7]
- There is insufficient evidence supporting benefit of safinamide in Unified Parkinson's Disease Rating Scale (UPDRS) part III (motor activity) scores in early stage PD as adjunct therapy to dopamine agonists based on three phase 3 trials.[8-11] This indication was denied approval by the FDA.[11]
- There is insufficient evidence to compare safinamide to any other anti-Parkinson's agents or evaluate differences in specific subpopulations.

Recommendations:

- Modify PA criteria (**Appendix 4**) to:
    - Add specific clinical criteria for safinamide which limits use to FDA-approved indication and
    - Add renewal criteria which requires physician attestation of condition improvement.
- After evaluation of comparative costs in executive session, no PDL changes were recommended.

Previous Conclusions:

- Since the previous Parkinson's disease drug class scan, there is limited new comparative evidence from one systematic review with meta-analysis and three randomized controlled trials. There are also two new levodopa and carbidopa formulations approved by the FDA for the treatment of Parkinson's disease and one new FDA safety alert.
- There is low quality evidence that levodopa monotherapy is more effective than levodopa-sparing therapy for improving activities of daily living and motor symptoms as measured by the UPDRS [Scale 0-176, 0 = no disability, 176 = worst disability; mean difference 0.95 (52 point scale), 95% CI, 0.51 to 1.39; p<0.0001 and 2.89 (108 point scale), 95% CI, 1.56 to 4.21; p<0.0001, respectively] but less effective than levodopa-sparing therapy for improvement of mental functioning [mean change from baseline -0.30 (16 point scale), 95% CI, -0.51 to -0.09; p=0.0005]. The clinical significance of these differences remain unclear.
- There is low quality evidence that levodopa monotherapy results in a worsening of motor complications compared to levodopa-sparing treatment (33.7% vs. 24.4%, respectively; p<0.0001), has increased risk of dyskinesia (RR 1.88, 95% CI, 1.37 to 2.59; p<0.0001), and higher incidence of wearing-off phenomenon (41.2% vs. 29.6%; p<0.00001). There is insufficient evidence of no difference in self-reported quality of life measurement scores between levodopa and levodopa-sparing therapy in the treatment of PD.

Previous Recommendations:

- No further review or research needed at this time. After the executive session, no changes in the PDL were made.

Background:

Parkinson's disease (PD) is a neurodegenerative disorder resulting in dopamine cell degeneration with a prevalence of up to 329 per 100,000 people.[12,13] The median age of onset is 60 years and men are 1.5 times more likely to develop PD than women.[14] PD is characterized by motor symptoms including akinesia, muscle rigidity, and tremor at rest.[13] PD may also be broken out into subtypes based on age of onset, motor phenotypes, cognitive impairments, or other non-motor symptoms.[15] While the onset of PD is gradual and early symptoms may be unnoticed or undiagnosed, it is a progressive disorder which results in significant disability.[14,16] The mean duration of disease from time of diagnosis to death is 15 years. [13]

Disease severity is commonly measured with the Hoehn and Yahr staging scale, which ranges from 1 to 5 with higher stages indicating greater disease severity.[17] Stage one indicates unilateral involvement typically with minimal or no functional disability, while stage 5 indicates confinement to bed or wheelchair unless aided.[17]

Nonpharmacologic therapies for the treatment of PD include exercise therapy and speech therapy.[18] Early pharmacologic treatment of PD includes levodopa/carbidopa and dopamine agonists such as ropinirole and pramipexole.[14,16] While dopaminergic therapies are initially effective, motor complications often develop over time.[19] One such motor complication is "off" time which is defined as periods of time when PD symptoms return as medication effect wears off.[19] This is in contrast to "on" time which is defined as time when PD motor symptoms are well controlled.[4] Commonly utilized medications for "off" time motor fluctuations are catechol-O-methyl transferase (COMT) inhibitors such as entacapone and tolcapone as well as monoamine oxidase B (MAO-B) inhibitors such as rasagiline, and selegiline.[19] Safinamide, which was approved in 2017, is also a MAO-B inhibitor.[20] In clinical trials, "on" and "off" time is commonly recorded through patient diaries.[4,5] It is unclear what is a clinically significant change in "on" or "off" time. In a Cochrane review on adjuvant treatment to levodopa in patients with PD with motor complications, COMT inhibitors and MAO-B inhibitors were found to reduce "off" time by 0.83 h/d and 0.93 h/d, respectively, compared to placebo.[21] Another motor complication is dyskinesia, or drug-induced involuntary movements, which can be treated by adjusting doses of existing therapies or adding amantadine.[1,19] While evidence is limited, amantadine may reduce dyskinesia by 24-45%.[19,22,23] Deep brain stimulation may also be considered for patients with symptoms inadequately controlled by medical therapy.[1]

The Unified Parkinson's Disease Rating Scale (UPDRS) assesses impairment and disability in PD and consists of four sections and 55 items.[3,24] Part I focuses on non-motor experiences of daily living which include mentation, behavior, and mood, Part II focuses on activities of daily living, Part III focuses on motor aspects, and Part IV focuses on complications of therapy.[3,24] Each item in each section is ranked on a 5-point scale and higher scores indicate more severe disease.[3] The minimum clinically important difference (MCID) in total UPDRS score is thought to be reduction of 4.1-4.5 points out of a total score of 199 points.[25,26] For UPDRS parts II and III specifically, the MCID is likely a reduction of around 2 points and 2.5-6 points, respectively, on scales that range from 0 to 52 and 0 to 108, respectively.[7,25,27,28] These two sections are most commonly seen as endpoints in recent clinical trials.[4,5] A validated modified UPDRS, the MDS-UPDRS, was established in 2008 by the Movement Disorder Society which retains the original scale's structure and provides clarity to ambiguities and also addresses additional factors of PD.[3,29]

There are a variety of different scales to classify severity of dyskinesias. The Unified Dyskinesia Rating Scale (UDysRS) is a 4-part scale which assesses dyskinesia.[30] Items on the scale are assessed from 0 to 4 with 0 indicating normal and 4 indicating severe.[30] Total scores can range from 0 to 104, with higher

scores indicating greater severity of dyskinesia.[30] Another dyskinesia scale, the Dyskinesia Rating Scale (DRS) also measures dyskinesia and scores can range from 0 to 48, with higher scores indicating greater severity of dyskinesia.[7,31] The MCID for the UDysRS and DRS is unclear.[7]

Quality of life in PD is often measured on the Parkinson's Disease Questionnaire (PDQ-39) which is a 39-item scale covering mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily comfort.[6] The maximum total score on the scale, which indicates worst health-related quality of life, is 800 with a maximum score of 100 in each of the 8 dimensions.[6,7] However, the total score can also be summarized into an index score (ranging from 0-100).[7] NICE guidance considers a change of 1.6 points in this index score to be a likely MCID indicating "a little worse".[6,7]

Fee-for-Service Utilization July 1, 2017 to September 30, 2017
In the third quarter of 2017, approximately 69% of pharmacy claims for anti-Parkinson's agents in the Oregon Medicaid Fee-For-Service (FFS) population were for the preferred agents which include benztropine, carbidopa/levodopa, carbidopa/levodopa/entacapone, entacapone, pramipexole, selegiline, and trihexyphenidyl.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Institute for Clinical and Economic Review (ICER), and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
No new moderate-high quality systematic reviews were identified. After review, 4 systematic reviews were excluded due to poor quality.[32-35]

New Guidelines:
National Institute for Health and Care Excellence (NICE)
In July 2017, an update to the 2006 guideline for PD in adults was published by NICE.[1] The major changes in this update include new recommendations on treating PD symptoms, deep brain stimulation, monitoring and managing impulse control disorders, and palliative care.[1] Recommendations regarding pharmacological treatment of motor symptoms include:

Management principles:

- Before starting treatment, discuss the patient's clinical circumstances, lifestyle circumstances, preferences, needs and goals, and the potential benefits and harms of the different drug classes (**Table 1**).[1]
- Anti-Parkinson's agents should not be withdrawn abruptly.[1]
- "Drug holidays" should not be taken with anti-Parkinson's agents due to risk of neuroleptic malignant syndrome.[1]

Table 1. Potential benefits and harms of levodopa, dopamine agonists, and MAO-B inhibitors[1] (adapted from the NICE guidelines)

	Levodopa	Dopamine Agonists	MAO-B Inhibitors
Motor Symptoms	More improvement in motor symptoms	Less improvement in motor symptoms	Less improvement in motor symptoms
Activities of Daily Living	More improvement in activities of daily living	Less improvement in activities of daily living	Less improvement in activities of daily living
Motor Complications	More motor complications	Fewer motor complications	Fewer motor complications
Adverse Events	Fewer specified adverse events*	More specified adverse events*	Fewer specified adverse events*

Abbreviations: MAO-B = monoamine oxidase B

*Specified adverse events include: excessive sleepiness, hallucinations, and impulse control disorders

First-line treatment:

- Offer levodopa to people in the early stages of PD whose motor symptoms impact their quality of life.[1]
- Consider a choice of dopamine agonists, levodopa, or MAO-B inhibitors for people in the early stages of PD whose motor symptoms do not impact their quality of life.[1]
- Do not offer ergot-derived dopamine agonists (such as cabergoline and bromocriptine) as first-line treatment for PD .[1]

Adjuvant treatment of motor symptoms:

- Offer a choice of dopamine agonists, MAO-B inhibitors, or COMT inhibitors as an adjunct to levodopa for people with PD who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy after discussing clinical and lifestyle circumstances as well as potential benefits and harms of different drug classes.[1]
- Choose a non-ergot-derived dopamine agonist in most cases, because of the monitoring that is needed with ergot-derived dopamine agonists.[1]
- Only consider an ergot-derived dopamine agonist as an adjunct to levodopa for people with PD who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy and whose symptoms are not adequately controlled with a non-ergot-derived dopamine agonist.[1]
- If dyskinesia is not adequately managed by modifying existing therapy, consider amantadine.[1]
- Do not offer anticholinergics to people with PD who have developed dyskinesia and/or motor fluctuations.[1]

New Formulations or Indications:

Gocovri™ (amantadine hydrochloride) (August 2017): A new extended-release (ER) capsule formulation of amantadine (Gocovri™) was approved for the treatment of dyskinesia in patients with PD receiving levodopa-based therapy, with or without concomitant dopaminergic medications.[2] The recommended

dosing is 137 mg daily for one week followed by the maintenance daily dose of 274 mg.[2] The daily dose is recommended to be taken at night in order to provide high levels of drug in the morning and daytime based on the pharmacokinetics.[36] Gocovri™ is the first medication approved by the FDA specifically for levodopa induced dyskinesia.[36]

Approval was based on two randomized, double-blind, placebo-controlled trials.[2] Key inclusion criteria for these trials were at least a mild functional impact of dyskinesia (score of ≥2 on part IV of the MDS-UPDRS) and at least 2 half-hour time intervals between 9am to 4pm of documented "on" time (periods when PD medications provide good benefit for motor symptoms) with troublesome dyskinesia for 2 consecutive days prior to day 1 of the study.[37,38] The mean age of patients in the trials was 64.8 years.[37,38] The primary endpoint in both trials was the change from baseline in total score of the UDysRS at week 12.[37,38] The maximum score for the UDysRS is 104 points, indicating maximum severity.[30]

In the first study, 63 patients received amantadine ER and 60 patients received placebo.[38] At baseline, the mean "on" time with troublesome dyskinesia at baseline was 4.6 hours and the mean UDysRS total score was 39.7.[38] At week 12, the mean change in UDysRS was -15.9 in the amantadine ER group and -8.0 in the placebo group (treatment difference: -7.9 points; 95% CI -12.5 to -3.3; p<0.001).[38] There were no serious drug-related adverse events (AEs) reported in either group, but a greater proportion of amantadine ER-treated patients discontinued treatment due to drug-related AEs compared to placebo patients (19.0% vs. 6.7%, respectively).[38] The most common AEs for amantadine- and placebo-treated patients were visual hallucinations (23.8% vs. 1.7%, respectively), peripheral edema (23.8% vs. 0%, respectively), dizziness (22.2% vs. 0%, respectively), and dry mouth (17.5% vs. 0%, respectively).[38]

In the second study, 37 patients received amantadine ER and 38 patients received placebo.[37] At baseline, the mean "on" time with troublesome dyskinesia at baseline was 5.4 hours and the mean UDysRS total score was 40.7.[37] At week 12, the mean change in UDysRS was -20.7 for the amantadine ER group and -6.3 for the placebo group (treatment difference: -14.4; 95% CI -20.4 to -8.3; p<0.0001).[37] One patient in the amantadine ER group experienced a study drug-related serious AE (2.7%) compared to no patients in the placebo group.[37] Additionally, a greater proportion of amantadine ER-treated patients discontinued treatment due to study drug-related AEs compared to placebo-treated patients (16.2% vs. 5.3%, respectively). The most common AEs reported for amantadine and placebo were dry mouth (13.5% vs. 2.6%, respectively), nausea (13.5% vs. 2.6%, respectively), decreased appetite (10.8% vs. 0%, respectively), insomnia (10.8% vs. 0%, respectively), and orthostatic hypotension (10.8% vs. 0%, respectively).[37]

Both trials were manufacturer-funded and had high overall attrition (>10%) for a relatively short (12 week) trial duration.[37,38] There is currently no evidence comparing immediate release and extended release amantadine formulations for dyskinesia in PD.

New FDA Safety Alerts:
No new safety alerts identified.

Randomized Controlled Trials:
A total of 102 citations were manually reviewed from the initial literature search. After further review, all 102 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

NEW DRUG EVALUATION: Xadago® (safinamide)

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Safinamide is a MAO-B inhibitor approved by the FDA as an adjunct treatment to levodopa/carbidopa in patients with PD experiencing "off" episodes.[20] Two clinical trials, Study-016 and SETTLE, contribute to the efficacy data for this indication.[4,5] Study-016 also has an 18 month extension study (Study-018).[39] While not FDA-approved for a second indication, 3 additional phase 3 trials (Study-015, Study-017, and MOTION) were conducted to study safinamide in early PD as adjunct to dopamine agonist therapy.[8-11] This indication of adjunct treatment to dopamine agonist therapy in early PD was ultimately not approved by the FDA, and therefore these studies will not be included in the comparative evidence table below.[11,20]

*Studies Evaluating Safinamide in the Mid-Late PD Population as an Adjunct to Levodopa (**Table 4**)*
Study-016 was a multicentered, randomized, double-blinded, placebo-controlled, parallel-group phase 3 trial in which patients were randomized 1:1:1 to safinamide 100 mg/day (n=224), safinamide 50 mg/day (n=223), or placebo (n=222) for 24 weeks.[5] Included patients had a diagnosis of idiopathic PD for at least 3 years, Hoehn and Yahr stages 1-4 during "off" periods, and motor fluctuations including over 1.5 hours of "off" time per day.[5] All patients took concomitant levodopa and the mean daily total "on" time with no or non-troublesome dyskinesia was 9.4 hours, with a mean UPDRS part III score of 28.1.[5] At week 24, benefit in the primary endpoint of change in mean daily total "on" time with no or non-troublesome dyskinesia was found for both the safinamide 100 mg group (mean difference 0.55 h/d; 95% CI 0.07-0.94; p=0.0223) and safinamide 50 mg group (mean difference 0.51 h/d; 95% CI 0.12-0.99; p=0.0130) compared to placebo.[5] A benefit was observed in quality of life, with change in total PDQ-39 score from baseline to week 24 with safinamide 100 mg (-28.4 points; 95% CI -31.9 to -1.1; p=0.0360) but not with safinamide 50 mg (-16.4 points; 95% CI -20.0 to 10.9; p=0.5603) compared to placebo (-11.9 points).[5] This manufacturer-funded fair quality trial had high overall attrition (11.2%) but had adequate concealment of allocation and blinding.[5] All of the treatment centers were located in India, Romania, or Italy, which limits applicability to the Oregon Medicaid population as well as U.S. patients in general.[5]

The SETTLE study was a double-blinded, placebo-controlled, parallel-group phase 3 trial in which patients were randomized 1:1 to either placebo (n=275) or safinamide 50 mg/day on days 1-13, followed by 100 mg/day starting on day 14 (n=274) if there were no tolerability issues, for a total of 24 weeks.[4] At day 14, 90.9% of the safinamide group and 94.1% in the placebo group were prescribed the 100 mg/day target dose.[4] Inclusion criteria were similar to Study-016.[4] All patients took concomitant levodopa with a mean dose of 776.6 mg/day. Mean Hoehn and Yahr stage was 2.5 (indicating moderate severity disease) and mean UPDRS part III score was 22.9.[4] At week 24, benefit in the primary endpoint of change from baseline to week 24 in mean daily "on" time without troublesome dyskinesia was found with safinamide (1.42 h/d; mean difference vs. placebo 0.96 h/d; 95% CI 0.56 to 1.37; p<0.001) compared to placebo (0.57 h/d).[4] Benefit was also seen in quality of life, measured by the PDQ-39 summary index score, with safinamide compared to placebo (-3.17 vs. -0.68 points, respectively; mean difference -2.49; 95% CI -3.98 to -0.68; p=0.006).[4] This manufacturer-funded fair quality trial had high overall attrition of 11.5% with adequate randomization and blinding.[4] Only 18% of patients were from North America, which may limit applicability to the Oregon Medicaid population.[4]

Study-018 was an 18-month multicentered, randomized, double-blind, placebo-controlled, parallel-group extension study of Study-016.[39] Patients who had completed Study-016 and were treatment compliant, or who had discontinued Study-016 but had completed efficacy evaluations at weeks 12 and 24 were included.[39] Patients continued in the same treatment group that they had been randomized to in Study-016.[39] Changes in concomitant PD medications were

allowed and because many patients had other medications increased, conclusions about efficacy may be limited.[11] At week 78, no benefit was found in the primary endpoint of mean change from baseline (defined as the start of Study-016) in total score of the Dyskinesia Rating Scale during "on" time with safinamide 100 mg/day (mean difference -0.59 h/d; 95% CI -1.40 to 0.21; p=0.1469) or safinamide 50 mg/day (mean difference -0.51 h/d; 95% CI -1.32 to 0.29; p=0.2125) compared to placebo.[39] However, there was a statistically significant benefit seen in the secondary endpoint of mean change from baseline to week 78 in total daily "on" time without troublesome dyskinesia with both safinamide 100 mg/day (mean difference -0.83 h/d; 95% CI 0.39 to 1.27; p=0.0002) and safinamide 50 mg/day (mean difference -0.67 h/d; 95% CI 0.23 to 1.11; p=0.0031) compared to placebo.[39] This poor quality manufacturer-funded trial had high overall attrition of 19.1% and high risk of reporting bias, as only differences versus placebo were reported rather than actual values for many of the secondary endpoints.[39]

Study-016, SETTLE, and Study-018 provide data to support efficacy of safinamide for idiopathic PD when used as an adjunct to levodopa for improvement of "off" episodes.[4,4,20] Improvement was seen in motor complications through total daily "on" time with no or non-troublesome dyskinesia.[4,4,20] Quality of life as measured by PDQ-39 scores was also improved.[4,5]

In February 2017, an evidence summary on PD with motor fluctuations with a focus on safinamide was published by NICE.[7] No recommendations specific to safinamide were made but NICE guidance on PD in adults (detailed previously in this review) was referenced and it was noted that choice of treatment should depend on patient characteristics and preferences after a discussion of risks and benefits with the patient.[1,7]

Studies Evaluating Safinamide in Early PD Population as Adjunct to Dopamine Agonist

Three phase 3 studies (Study-015, Study-017, and MOTION) were completed studying safinamide in early PD as an add-on therapy to dopamine agonists, which is an indication ultimately not approved by the FDA due to insufficient efficacy evidence.[8-11] Patients in all three studies were required to be on single dopamine agonist therapy (which does not include levodopa) and Study-015 excluded patients on additional PD medications other than a single dopamine agonist.[8-10] The primary outcome in Study-015 was change in UPDRS part III (motor examination) total score from baseline to week 24.[9] There was no change in the primary outcome with safinamide 200 mg per day versus placebo (-3.9 vs. -3.6, respectively; 95% CI -2.3 to 1.4; p=0.65) but there was a benefit seen with safinamide 100 mg per day versus placebo (-6.0 vs. -3.6, respectively; 95% CI -3.7 to -0.1; p=0.0419).[9] However, the FDA notes that pre-specified hierarchical statistical comparison was documented in the statistical analysis plan requiring comparison of the 200 mg strength prior to the 100 mg strength.[9,11] Therefore, statistical testing could not be formally conducted for the 100 mg dose as the 200 mg dose did not show statistically significant results.[9,11]

Study-017 was a 12-month randomized, double-blind, placebo-controlled extension study of Study-015.[8] The primary endpoint was time from baseline (randomization in Study-015) to an "intervention" which was defined as an increase in the dose of dopamine agonist; addition of another dopamine agonist, levodopa, or other PD treatment; or discontinuation due to lack of efficacy.[8] No benefit was seen in the primary endpoint with the safinamide groups (pooled doses) versus placebo (559 days vs. 466 days, respectively; p=0.3342).[8] Change in UPDRS part III scores was a secondary endpoint and no benefit was seen with safinamide (pooled doses) versus placebo (-3.0 vs. -1.7, respectively; p=0.1893).[8] Similarly, in the MOTION trial, there was no significant benefit in change from baseline to week 24 of UPDRS part III with safinamide 50 mg/day versus placebo (least squares mean difference vs. placebo -0.65; p=0.259) or 100 mg/day versus placebo (least squares mean difference vs. placebo -1.04; p=0.073).[10,11]

Based on these 3 trials, the FDA determined that there was not sufficient evidence to support approval of safinamide in the early PD population as adjunct to dopamine agonist therapy.[11]

Clinical Safety:
The most common adverse events in Study-016 and SETTLE associated with safinamide 100 mg/day where the incidence for safinamide was at least 2% greater than for placebo include dyskinesia, fall, nausea, and insomnia (**Table 2**).[4,4,20]

Table 2. Selected Adverse Reactions with an Incidence of ≥2% with Safinamide 100 mg/day and Greater than Placebo

	Safinamide 50 mg/day (n=223)	Safinamide 100 mg/day (n=498)	Placebo (n=497)
Dyskinesia	21%	17%	9%
Fall	4%	6%	4%
Nausea	3%	6%	4%
Insomnia	1%	4%	2%

Serious adverse events (SAE) occurred in 9.8% (n=22) and 8.1% (n=18) of patients treated with safinamide 100 mg/day and placebo, respectively in Study-016.[5] No specific pattern of SAEs was determined.[5] In SETTLE, 9.5% (n=26) and 6.6% (n=18) of safinamide- and placebo-treated patients experienced SAEs.[4] SAEs which occurred in more than one safinamide-treated patient included breast cancer (n=2) and visual hallucinations (n=2).[4]

Dyskinesia was the most commonly reported AE in both Study-016 and SETTLE.[4,5] The incidence was 21.1%, 18.3%, and 12.6% in the safinamide 50 mg/day, safinamide 100 mg/day, and placebo groups in Study-016.[5] However, severe dyskinesia was only reported in 0.9%, 1.8%, and 2.3% of those same groups.[5] In SETTLE, the incidence overall was 14.6% in the safinamide group compared to 5.5% in the placebo group, but only reported as severe in 1.8% and 0.4% in those same groups, respectively.[4]

In long-term extension trial data, the percent of patients experiencing newly treatment-emergent AEs (TEAEs) in Study-018 for safinamide 100 mg/day, safinamide 50 mg/day, and placebo groups were 78.3%, 76.7%, and 85.1%, respectively.[33] For those same groups, serious TEAEs occurred in 18.9%, 16.9%, and 16.0% of patients.[39] During the 2-year treatment period of Study-016 and Study-018 combined, worsening of PD and dyskinesia were the most frequent TEAEs.[33] Worsening of PD was reported in 23.9%, 22.2%, and 24.0% of patients treated with safinamide 100 mg/day, safinamide 50 mg/day, and placebo, respectively. Dyskinesia was reported in 27.8%, 31.2%, and 21.7% of those groups, respectively.[33] Discontinuation due to TEAEs occurred in 6.7%, 5.3%, and 5.7% of the safinamide 100 mg/day, safinamide 50 mg/day, and placebo groups. [33]

Per FDA labeling, safinamide is contraindicated in patients with concomitant use of other MAO inhibitors, opioids, and dextromethorphan and patients with a history of hypersensitivity to safinamide or in severe hepatic impairment (Child-Pugh C).[20]

Look-alike / Sound-alike Error Risk Potential: none identified.

Table 3. Pharmacology and Pharmacokinetic Properties.[20]

Parameter	
Mechanism of Action	Inhibition of monoamine oxidase B (MAO-B), which blocks the catabolism of dopamine
Oral Bioavailability	95%
Distribution and Protein Binding	165 L volume of distribution; not highly protein bound (unbound fraction of 11-12%)
Elimination	Metabolism through 3 main pathways; none of metabolites have pharmacological activity; ~5% eliminated unchanged, mainly in urine
Half-Life	20-26 hours
Metabolism	Hydrolytic oxidation, oxidative cleavage, and conjugation with glucuronic acid

Abbreviations: L = liter

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Symptom improvement ("on" time, "off" time, UPDRS, UDysRS, DRS)
2) Quality of life (PDQ-39)
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Total daily "on" time

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Borgohain R, et al[5] STUDY-016 Phase 3, randomized, MC, DB, PC, PG	1. Safinamide 100 mg/d 2. Safinamide 50 mg/d 3. Placebo 4 phases: • 10 d screening period • 4 wk L-dopa stabilizat-ion period	Demographics: -Age: 59.9 y -Male: 71.8% -Asian: 80.6% -White: 19.4% -Mean Hoehn & Yahr stage: 2.8 -Concomitant L-dopa: 100% -Concomitant dopamine agonist: 60.8% -Concomitant anticholinergic: 37.1% -Mean daily total "on" time with no or non-troublesome dyskinesia: 9.4 h	ITT: Total: 669 1. 224 2. 223 3. 222 Attrition: Total: 11.2% 1. 29 (12.9%) 2. 21 (9.4%) 3. 25 (11.3%)	Primary Endpoint: Change in mean daily total "on" time with no or non-troublesome dyskinesia at week 24: 1. 1.36 ±2.625 h 2. 1.37 ±2.745 h 3. 0.97 ±2.375 h *1 vs. 3:* LS mean change: 0.55 h (95% CI, 0.07-0.94); P=0.0223 *2 vs. 3:* LS mean change: 0.51 h (95% CI, 0.12-0.99); P=0.0130 Secondary Endpoints: (reported as change from baseline to week 24) Change in total daily "off" time: 1. -1.3 h 2. -1.3 h 3. -0.7 h	 NA NA	Study drug-related AE: 1. 67 (29.9%) 2. 69 (30.9%) 3. 51 (23.0%) P=0.1395 RR & 95% CI NR Serious AE: 1. 22 (9.8%) 2. 8 (3.6%) 3. 18 (8.1%) P=0.0286 RR & 95% CI NR DC due to AE:	 NA NA NA 4.5% /23	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomization by computer-generated randomization schedule, administered by central IVRS. Baseline characteristics balanced. Performance Bias: Low. Safinamide and placebo identical in appearance. Protocol approved in all countries studied. Detection Bias: Low. Investigators, patients, and caregivers blinded to treatment. Attrition Bias: High. Overall attrition >10%. MMRM analysis utilized for primary endpoint with

	• 24 wk treatment period • Optional 1 wk taper period Randomized 1:1:1	-Mean UPDRS-III: 28.1 Key Inclusion Criteria: -30-80 y of age -idiopathic PD ≥3 y -Hoehn & Yahr stage I-IV during "off" -motor fluctuations (>1.5 h "off" time/d) Key Exclusion Criteria: -late-stage PD with severe, disabling peak-dose or biphasic dyskinesia -late-stage PD with unpredictable or widely swinging symptom fluctuation -dementia, major psychiatric illnesses, severe and progressive medical illnesses		*1 vs. 3:* LS mean difference: -0.6 h (95% CI, -1.0 to -0.2); P=0.0034 *2 vs. 3:* LS mean difference: -0.6 h (95% CI, -0.9 to -0.2); P=0.0043 Change in UPDRS Part III (motor) scores during "on": 1. -6.9 2. -6.1 3. -4.3 *1 vs. 3:* LS mean change: -2.6 (95% CI, -4.1 to -1.1); P=0.0006 *2 vs. 3:* LS mean change: -1.8 (95% CI, -3.3 to -0.4); P=0.0138 Change in UPDRS Part II (activities of daily living) scores during "on": 1. -2.2 2. -1.7 3. -1.2 *1 vs. 3:* -1.0 (95% CI, -1.7 to -0.3); P=0.0060 *2 vs. 3:* -0.5 (95% CI, -1.2 to 0.2); P=0.1253 Change in "off" time following first morning L-dopa dose: 1. -1.2 h 2. -1.1 h 3. -0.6 h *1 vs. 3:* -0.6 h (95% CI, -1.0 to -0.2); P=0.0011 *2 vs. 3:* -0.5 h (95% CI, -0.9 to -0.2); P=0.0031 Change in PDQ-39 total score: 1. -28.4 2. -16.4 3. -11.9 *1 vs. 3:* -16.5 (95% CI, -31.9 to -1.1); P=0.0360 *2 vs. 3:* -4.5 (95% CI, -20.0 to 10.9); P=0.5603	NA NA NA NA NS NA NA NA NS	1. 14 (6.3%) 2. 11 (4.9%) 3. 12 (5.4%) P=0.8497 RR & 95% CI NR Dyskinesia: 1. 41 (18.3%) 2. 47 (21.1%) 3. 28 (12.6%) RR, 95% CI, & p-value NR Severe dyskinesia: 1. 1.8% 2. 0.9% 3. 2.3% RR, 95% CI, & p-value NR	NA NA NA NA NA NA	no imputations for missing data. ITT analysis used. Reporting Bias: Unclear. All primary and secondary efficacy endpoints reported, although study protocol not available. Funded by Newron and Merck Serono. **Applicability**: Patient: Broad exclusion criteria limits applicability to more severe disease or patients with significant comorbid conditions. Intervention: Safinamide dose appropriate and approved by the FDA. Comparator: A MAO-B inhibitor comparator would have been a more meaningful comparison than placebo. Outcomes: Outcomes appropriate for condition. Setting: 52 treatment centers in India (35), Romania (10), and Italy (7). May limit applicability to the U.S. population.
2. Schapira, et al[4] SETTLE DB, PG, PC, phase 3 trial	1. Safinamide 50 mg/d for days 1-13, then 100 mg/d starting on day 14 if no tolerability issues	Demographics: -Age: 61.9 y -Male: 60.9% -White: 67.6% -North America: 18.6% -Western Europe: 39.9%	ITT: Total: 549 1. 274 2. 275 Attrition: Total: 63 (11.5%)	Primary Endpoint: Change from baseline to week 24 in mean daily "on" time without troublesome dyskinesia: 1. +1.42 h/d 2. +0.57 h/d LS mean difference: 0.96 h/d (95% CI, 0.56 to 1.37); P<0.001	 NA	Study drug-related AE: 1. 78 (28.5%) 2. 76 (27.6%) Serious AE: 1. 18 (6.6%) 2. 26 (9.5%)	 NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomization and allocation via computerized central IVRS. Baseline characteristics balanced. Performance Bias: Low. Placebo was provided as matching tablets

	2. Placebo daily 24 weeks Randomized 1:1	-Mean Hoehn & Yahr stage: 2.5 -Mean levodopa dose: 776.6 mg/d -Mean Part II UPDRS Score: 10.2 -Mean Part III UPDRS Score: 22.9 <u>Key Inclusion Criteria</u>: -30-80 y of age -idiopathic PD ≥3 y -Hoehn & Yahr stage I-IV during "off" -motor fluctuations (>1.5 h "off" time/d) -L-dopa responsive and on stable regimen x4w <u>Key Exclusion Criteria</u>: -severe, disabling peak-dose or biphasic dyskinesia -wide or unpredictable symptom fluctuations -current diagnosis of a clinically significant medical condition other than PD	1. 29 (10.6%) 2. 34 (12.4%)	<u>Secondary Endpoints</u>: Change in "off" time from baseline to week 24: 1. -1.56 h/d 2. -0.54 h/d LS mean difference: -1.03 (95% CI, -1.40 to -0.67); P<0.001 Change in UPDRS Part III score from baseline to week 24: 1. -3.43 2. -1.83 LS mean difference: -1.82 (95% CI, -3.01 to -0.62); P=0.003 Change in UPDRS Part II score from baseline to week 24: 1. -1.07 2. -0.75 LS mean difference: -0.43 (95% CI, -1.02 to 0.16); P=0.15 Patients with improvement on CGI-C (scores of 1-3): 1. 57.7% 2. 41.8% LS mean difference: 1.92 (95% CI, 1.36 to 2.70); P<0.001 Change from baseline to week 24 in PDQ-39 summary index score: 1. -3.17 2. -0.68 LS mean difference: -2.33 (95% CI, -3.98 to -0.68); P=0.006	NA NA NS 15.9 %/7 NA	<u>Study drug-related serious AE:</u> 1. 3 (1.1%) 2. 6 (2.2%) <u>DC due to AE:</u> 1. 12 (4.4%) 2. 10 (3.6%) <u>Deaths:</u> 1. 1 (0.4%) 2. 2 (0.7%) <u>Dyskinesia:</u> 1. 40 (14.6%) 2. 15 (5.5%) RR, 95% CI, & p-value NR	NA NA NA NA	in matching blister packs. Protocol approved at each center. <u>Detection Bias</u>: Low. Study site personnel and patients blinded. <u>Attrition Bias</u>: High. Overall attrition >10%. LOCF approach to missing data utilized for a chronic, deteriorating condition. ITT analysis. <u>Reporting Bias</u>: Unclear. Protocol available. All primary and secondary outcomes reported on. Funded by Newron and Merck Serono. The funder was involved in collection, management, analysis, and interpretation of data as well as preparation and review of the manuscript. **Applicability**: <u>Patient</u>: Broad exclusion criteria limits applicability to more severe disease or patients with significant comorbid conditions. <u>Intervention</u>: Safinamide dose appropriate. <u>Comparator</u>: A MAO-B inhibitor comparator would have been a more meaningful comparison than placebo. <u>Outcomes</u>: Outcomes appropriate for condition. <u>Setting</u>: Only 18% of patients were from North America. The majority of patients were from western Europe or the Asia-Pacific region.

<u>Abbreviations</u> [alphabetical order]: AE = adverse event; ARR = absolute risk reduction; CGI-C = Clinical Global Impression-Change; CI = confidence interval; d = day; DB = double-blind; DC = discontinuation; DRS = Dyskinesia Rating Scale; h = hour; ITT = intention to treat; IVRS = interactive voice-response system; L-dopa = levodopa; LS = least squares; MC = multicenter; mg/d = milligrams per day; mITT = modified intention to treat; MMRM = mixed model repeated measures; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR= not reported; NS = not significant; PC = placebo controlled; PD = Parkinson's disease; PDQ-39 = Parkinson's Disease Questionnaire; PG = parallel-group; PP = per protocol; TEAE = treatment-emergent adverse event; wk = week; Y = years

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Appendix 1: Current Preferred Drug List

PDL	Generic	Brand	Route	Form
Y	PRAMIPEXOLE DI-HCL	MIRAPEX	ORAL	TABLET
Y	PRAMIPEXOLE DI-HCL	PRAMIPEXOLE DIHYDROCHLORIDE	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA	CARBIDOPA-LEVODOPA	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA	SINEMET 10-100	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA	SINEMET 25-100	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA	SINEMET 25-250	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA	CARBIDOPA-LEVODOPA ER	ORAL	TABLET ER
Y	CARBIDOPA/LEVODOPA	SINEMET CR	ORAL	TABLET ER
Y	SELEGILINE HCL	SELEGILINE HCL	ORAL	CAPSULE
Y	ENTACAPONE	COMTAN	ORAL	TABLET
Y	ENTACAPONE	ENTACAPONE	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA/ENTACAPONE	CARBIDOPA-LEVODOPA-ENTACAPONE	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA/ENTACAPONE	STALEVO 150	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA/ENTACAPONE	STALEVO 100	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA/ENTACAPONE	STALEVO 50	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA/ENTACAPONE	STALEVO 200	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA/ENTACAPONE	STALEVO 75	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA/ENTACAPONE	STALEVO 125	ORAL	TABLET
Y	TRIHEXYPHENIDYL HCL	TRIHEXYPHENIDYL HCL	ORAL	ELIXIR
Y	TRIHEXYPHENIDYL HCL	TRIHEXYPHENIDYL HCL	ORAL	TABLET
Y	BENZTROPINE MESYLATE	BENZTROPINE MESYLATE	ORAL	TABLET
N	CARBIDOPA	CARBIDOPA	ORAL	TABLET
N	CARBIDOPA	LODOSYN	ORAL	TABLET
N	AMANTADINE HCL	AMANTADINE	ORAL	CAPSULE
N	AMANTADINE HCL	AMANTADINE	ORAL	SOLUTION
N	AMANTADINE HCL	AMANTADINE	ORAL	TABLET
N	BROMOCRIPTINE MESYLATE	BROMOCRIPTINE MESYLATE	ORAL	CAPSULE
N	BROMOCRIPTINE MESYLATE	PARLODEL	ORAL	CAPSULE
N	BROMOCRIPTINE MESYLATE	BROMOCRIPTINE MESYLATE	ORAL	TABLET
N	BROMOCRIPTINE MESYLATE	PARLODEL	ORAL	TABLET
N	ROPINIROLE HCL	REQUIP	ORAL	TABLET
N	ROPINIROLE HCL	ROPINIROLE HCL	ORAL	TABLET
N	ROPINIROLE HCL	REQUIP XL	ORAL	TAB ER 24H
N	ROPINIROLE HCL	ROPINIROLE ER	ORAL	TAB ER 24H
N	PRAMIPEXOLE DI-HCL	MIRAPEX ER	ORAL	TAB ER 24H
N	PRAMIPEXOLE DI-HCL	PRAMIPEXOLE ER	ORAL	TAB ER 24H

N	CARBIDOPA/LEVODOPA	CARBIDOPA-LEVODOPA	ORAL	TAB RAPDIS
N	CARBIDOPA/LEVODOPA	RYTARY	ORAL	CAPSULE ER
N	TOLCAPONE	TASMAR	ORAL	TABLET
N	TOLCAPONE	TOLCAPONE	ORAL	TABLET
N	SELEGILINE HCL	SELEGILINE HCL	ORAL	TABLET
N	SELEGILINE HCL	ZELAPAR	ORAL	TAB RAPDIS
N	RASAGILINE MESYLATE	AZILECT	ORAL	TABLET
N	RASAGILINE MESYLATE	RASAGILINE MESYLATE	ORAL	TABLET
N	ROTIGOTINE	NEUPRO	TRANSDERM	PATCH TD24
N	SAFINAMIDE MESYLATE	XADAGO	ORAL	TABLET
N	AMANTADINE HCL	GOCOVRI	ORAL	CAP ER 24H

Appendix 2: Medline Search Strategy on 1/3/2018

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
1 pramipexole.mp. 1544
2 exp Carbidopa/ 2408
3 exp Levodopa/ 16907
4 exp Selegiline/ 2482
5 entacapone.mp 675
6 exp Trihexyphenidyl/ 956
7 exp Benztropine/ 735
8 exp Amantadine/ 5987
9 exp Bromocriptine/ 7598
10 ropinirole.mp. 954
11 tolcapone.mp. 479
12 rasagiline.mp. 680
13 rotigotine.mp. 573
14 safinamide.mp. 136
15 Parkinson Disease/ or Antiparkinson Agents/ or antiparkinson.mp. 68001
16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 36314
17 15 and 16 12495
18 limit 17 to (English language and humans and yr="2016 –Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 102

Appendix 3: Prescribing Information Highlights for Safinamide[20]

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XADAGO safely and effectively. See full prescribing information for XADAGO.

XADAGO (safinamide) tablets, for oral use
Initial U.S. Approval: 2017

----------**INDICATIONS AND USAGE**----------
XADAGO is a monoamine oxidase type B (MAO-B) inhibitor indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes (1)

Limitations of Use: XADAGO has not been shown to be effective as monotherapy for the treatment of PD.

----------**DOSAGE AND ADMINISTRATION**----------
- Start with 50 mg administered orally once daily at the same time of day; after two weeks, the dose may be increased to 100 mg once daily, based on individual need and tolerability (2.1)
- Hepatic Impairment: Do not exceed 50 mg once daily in patients with moderate hepatic impairment; contraindicated in patients with severe hepatic impairment (2.2, 4)

----------**DOSAGE FORMS AND STRENGTHS**----------
Tablets: 50 mg and 100 mg (3)

----------**CONTRAINDICATIONS**----------
XADAGO is contraindicated in patients with:
- Concomitant use of the following drugs:
  - Other monoamine oxidase inhibitors or other drugs that are potent inhibitors of monoamine oxidase (e.g., linezolid) (4, 7.1)
  - Opioid drugs (e.g., tramadol, meperidine and related derivatives); selective norepinephrine reuptake inhibitors; tri-or tetra-cyclic or triazolopyridine antidepressants; cyclobenzaprine; methylphenidate, amphetamine, and their derivatives; St. John's wort (4, 7.2, 7.3, 7.5)
  - Dextromethorphan (4, 7.4)
- A history of a hypersensitivity to safinamide (4)
- Severe hepatic impairment (Child-Pugh C: 10-15) (4)

----------**WARNINGS AND PRECAUTIONS**----------
- May cause or exacerbate hypertension (5.1)
- May cause serotonin syndrome when used with MAO inhibitors, antidepressants, or opioid drugs (5.2)
- May cause falling asleep during activities of daily living (5.3)
- May cause or exacerbate dyskinesia; consider levodopa dose reduction (5.4)
- May cause hallucinations and psychotic behavior (5.5)
- May cause problems with impulse control/compulsive behaviors (5.6)
- May cause withdrawal-emergent hyperpyrexia and confusion (5.7)

----------**ADVERSE REACTIONS**----------
Most common adverse reactions (incidence on XADAGO 100 mg/day at least 2% greater than placebo) were dyskinesia, fall, nausea, and insomnia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact US WorldMeds, LLC, Inc. at 1-888-492-3246 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------**DRUG INTERACTIONS**----------
- Selective Serotonin Reuptake Inhibitors: Monitor patients for serotonin syndrome (7.3)
- Sympathomimetic Medications: Monitor patients for hypertension (7.5)
- Tyramine: Risk of severe hypertension (7.6)
- Substrates of Breast Cancer Resistance Protein (BCRP): Potential increase in plasma concentration of BCRP substrate (7.7)

----------**USE IN SPECIFIC POPULATIONS**----------
Pregnancy: Based on animal data, may cause fetal harm (8.1).

See Section 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 3/2017

Anti-Parkinson's Agents

Goals:

- Promote preferred drugs for Parkinson's disease.
- Restrict use for non-funded conditions (e.g., restless leg syndrome).
- To limit utilization of safinamide to FDA-approved indications.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis Parkinson's disease or another chronic neurological condition?	**Yes:** Go to #5	**No:** Go to #3
3. Is the diagnosis Restless Leg Syndrome?	**Yes:** Pass to RPh. Deny; not funded by the OHP.	**No:** Go to #4
4. RPh only: All other indications need to be evaluated to determine if treatment is for a funded condition.	**Funded:** Go to #5	**Not Funded:** Deny; not funded by the OHP.
5. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**.	**No:** Go to #6.

Approval Criteria		
6. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #7
7. Does the patient have a diagnosis of Parkinson's disease and experiences "off" episodes?	**Yes:** Go to #8	**No:** Approve for the shorter of 1 year or length of prescription.
8. Is the request for safinamide?	**Yes:** Go to #9	**No:** Approve for the shorter of 1 year or length of prescription.
9. Is the patient currently taking levodopa/carbidopa?	**Yes:** Approve for the shorter of 1 year or length of prescription.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing physician and physician attests to patient's improvement?	**Yes:** Approve for the shorter of 1 year or length of prescription.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T Review: *3/18 (JP); 7/16; 9/14; 9/13; 09/10*
Implementation: *4/16/18; 8/16, 1/1/14, 1/1/11*