

## 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 define place in therapy for 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, or concomitant therapies for which one anti-Parkinson's agent is better tolerated or more effective than other available biologics 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.<sup>1</sup> 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, with or without concomitant dopaminergic medications was identified since the time of last review.<sup>2</sup> No new safety alerts or comparative evidence of anti-Parkinson's agents were identified.
- There is low quality of evidence that safinamide 100 mg improves total daily "on" time with no or non-troublesome dyskinesia compared to placebo at 24 weeks (Study-016: +1.36 hours/day (h/d); mean change vs. placebo 0.55h/d; 95% CI 0.07-0.94; p=0.0223; SETTLE study: +1.42 h/d; mean difference vs. placebo 0.96 h/d; 95% CI 0.56 to 1.37; p<0.001).<sup>3,4</sup> "On" time is defined as time when PD motor symptoms are well controlled.<sup>3</sup>

- There is low quality of evidence that safinamide 100 mg improves total daily “off” time compared to placebo at 24 weeks (Study-016: -1.3h/d; mean change vs. placebo -0.6h/d; 95% CI -1.0 to -0.2; p=0.0034; SETTLE study: -1.56 h/d; mean difference vs. placebo -1.03h/d; 95% CI -1.40 to -0.67; p<0.001).<sup>3,4</sup> “Off” time is defined as periods of time when PD motor symptoms return as levodopa’s effect wears off.<sup>5</sup>
- There is low quality of evidence that safinamide 100 mg 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; 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).<sup>3,4</sup> 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.<sup>6,20</sup> A minimum clinically important difference on the PDQ-39 summary index is considered to be around 1.6 points.<sup>6,20</sup>
- 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.<sup>7-10</sup> This indication was denied approval by the FDA.<sup>10</sup>
- There is insufficient evidence to compare safinamide to any other anti-Parkinson’s agents.

#### **Recommendations:**

- Continue to apply clinical prior authorization (PA) to safinamide. Apply criteria to limit use to FDA-approved indication (**Appendix 5**).
- Evaluate comparative costs in executive session.

#### **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.<sup>11,12</sup> The median age of onset is 60 years and men are 1.5 times more likely to develop PD than women.<sup>13</sup> PD is characterized by motor symptoms including akinesia,

muscle rigidity, and tremor at rest.<sup>12</sup> 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.<sup>13,14</sup> The mean duration of disease from time of diagnosis to death is 15 years.<sup>13</sup>

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.<sup>15</sup> Stage one indicates unilateral involvement typically with minimal or no functional disability, while stage 5 indicates confinement to bed or wheelchair unless aided.<sup>15</sup>

Nonpharmacologic therapies for the treatment of PD include exercise therapy and speech therapy.<sup>16</sup> Early pharmacologic treatment of PD includes dopaminergic agents such as levodopa/carbidopa, cabergoline, ropinirole, and pramipexole.<sup>14</sup> While dopaminergic therapies are initially effective, motor complications often develop over time.<sup>5</sup> One such motor complication is “off” time which is defined as periods of time when PD symptoms return as medication effect wears off.<sup>5</sup> This is in contrast to “on” time which is defined as time when PD motor symptoms are well controlled.<sup>3</sup> 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.<sup>5</sup> Safinamide, which was approved in 2017, is also a MAO-B inhibitor.<sup>32</sup> In clinical trials, “on” and “off” time is commonly recorded through patient diaries.<sup>3,4</sup> Another motor complication is dyskinesia, or drug-induced involuntary movements, which can be treated by amantadine.<sup>5</sup> Deep brain stimulation may also be considered for patients with symptoms inadequately controlled by medical therapy.<sup>1</sup>

The Unified Parkinson’s Disease Rating Scale (UPDRS) assesses impairment and disability in PD and consists of four sections and 55 items.<sup>17,18</sup> 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.<sup>17,18</sup> Each item in each section is ranked on a five-point scale and higher scores indicate more severe disease.<sup>18</sup> The minimum clinically important difference in total UPDRS score is thought to be reduction of 4.1-4.5 points.<sup>19</sup> For UPDRS part II and III specifically, the minimum clinically important difference is likely a reduction of around 2 points and 2.5-6 points, respectively.<sup>19-22</sup> A 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.<sup>18,23</sup>

The Unified Dyskinesia Rating Scale (UDysRS) is a four part scale which assesses dyskinesia.<sup>24</sup> Items on the scale are assessed from 0 to 4 with 0 indicating normal and 4 indicating severe.<sup>24</sup> Total scores can range from 0 to 104, with higher scores indicating greater severity of dyskinesia.<sup>24</sup> 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.<sup>20,25</sup> The minimal clinically important difference for the DRS is unclear.<sup>20</sup>

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.<sup>6</sup> 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.<sup>6,20</sup> However the total score can also be summarized into an index score (ranging from 0-100), and a minimum clinically important difference indicating “a little worse” correlates to an change of 1.6 points in this index score.<sup>6,20</sup>

#### **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.<sup>26-29</sup>

**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.<sup>1</sup> 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.<sup>1</sup> 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.<sup>1</sup>
- Anti-Parkinson agents should not be withdrawn abruptly or allowed to fail suddenly due to poor absorption.<sup>1</sup>
- "Drug holidays" should not be taken due to risk of neuroleptic malignant syndrome.<sup>1</sup>

## First-line treatment:

- Offer levodopa to people in the early stages of PD whose motor symptoms impact their quality of life.<sup>1</sup>
- Consider a choice of dopamine agonists, levodopa, or monoamine oxidase B (MAO-B) inhibitors for people in the early stages of PD whose motor symptoms do not impact their quality of life.<sup>1</sup>
- Do not offer ergot-derived dopamine agonists as first-line treatment for PD.<sup>1</sup>

## Adjuvant treatment of motor symptoms:

- Offer a choice of dopamine agonists, MAO-B inhibitors, or catechol-O-methyl transferase (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.<sup>1</sup>
- Choose a non-ergot-derived dopamine agonist in most cases, because of the monitoring that is needed with ergot-derived dopamine agonists.<sup>1</sup>
- 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.<sup>1</sup>
- If dyskinesia is not adequately managed by modifying existing therapy, consider amantadine.<sup>1</sup>
- Do not offer anticholinergics to people with PD who have developed dyskinesia and/or motor fluctuations.<sup>1</sup>

#### **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.<sup>2</sup> The recommended dosing is 137 mg daily for one week followed by the maintenance daily dose of 274 mg.<sup>2</sup> Approval was based on two randomized, double-blind, placebo-controlled trials.<sup>2</sup> Key inclusion criteria for these trials were at least a mild functional impact of dyskinesia (score of  $\geq 2$  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.<sup>30,31</sup> The mean age of patients in the trials was 64.8 years.<sup>30,31</sup> The primary endpoint in both trials was the change from baseline in total score of the UDysRS at week 12.<sup>30,31</sup> The maximum score for the UDysRS is 104 points, indicating maximum severity.<sup>24</sup>

In the first study, 63 patients were randomized to and received amantadine ER and 60 patients were randomized to and received placebo.<sup>31</sup> At baseline, the mean “on” time with troublesome dyskinesia at baseline was 4.6 hours and the mean UDysRS total score was 39.7.<sup>31</sup> 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;  $p < 0.001$ ).<sup>31</sup> There were no study drug-related serious adverse events (AEs) reported in either group, but a greater proportion of amantadine ER-treated patients discontinued treatment due to study drug-related AEs compared to placebo-treated patients (19.0% vs. 6.7%, respectively).<sup>31</sup> The most common AEs for amantadine and placebo-treated patients included 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).<sup>31</sup>

In the second study, 37 patients were randomized to and received amantadine ER and 38 patients were randomized to and received placebo.<sup>30</sup> At baseline, the mean “on” time with troublesome dyskinesia at baseline was 5.4 hours and the mean UDysRS total score was 40.7.<sup>30</sup> 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;  $p < 0.0001$ ).<sup>30</sup> One patient in the amantadine ER group experienced a study drug-related serious AE (2.7%) compared to no patients in the placebo group.<sup>30</sup> 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).<sup>30</sup>

Both trials were manufacturer-funded and had high overall attrition (>10%) for a relatively short (12 week) trial duration.<sup>30,31</sup>

**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 monoamine oxidase type B (MAO-B) inhibitor FDA-approved as an adjunct treatment to levodopa/carbidopa in patients with PD experiencing “off” episodes.<sup>32</sup> Two clinical trials, Study-016 and SETTLE, contribute to the efficacy data for this indication.<sup>3,4</sup> Study-016 also has an 18 month extension study (Study-018).<sup>33</sup> While not FDA-approved for another indication, 3 additional phase 3 trials (Study-015, Study-017, and MOTION) were conducted to study safinamide as adjunct to dopamine agonist therapy.<sup>7-10</sup> This indication was ultimately not approved by the FDA, and therefore these studies will not be included in the comparative evidence table below.<sup>10,32</sup>

#### *Studies Evaluating Safinamide in the Mid-Late PD Population as an Adjunct to Levodopa (Table 2)*

Study-016 was a multicenter, double-blinded, placebo-controlled, parallel-group, randomized 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.<sup>4</sup> Included patients had a diagnosis of idiopathic PD for at least 3 years, Hoehn and Yahr stage I-IV during “off” periods, and motor fluctuations including over 1.5 hours of “off” time per day.<sup>4</sup> The average age of the patients was 59.9 years, 71.8% were male, and 80.6% of the patients were Asian. 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.<sup>4</sup> At week 24, there was a significant benefit in the primary endpoint of change in mean daily total “on” time with no or non-troublesome dyskinesia for both the safinamide 100 mg (mean change 0.55h; 95% CI 0.07-0.94; p=0.0223) and safinamide 50 mg (mean change 0.51h; 95% CI 0.12-0.99; p=0.0130) compared to placebo.<sup>4</sup> There was also a statistically significant benefit seen in the secondary endpoint of change from baseline in total daily “off” time at week 24 with safinamide 100 mg (mean change -0.6h; 95% CI -1.0 to -0.2; p=0.0034) and safinamide 50 mg (mean change -0.6h; 95% CI -0.9 to -0.2; p=0.0043) compared to placebo.<sup>4</sup> In terms of quality of life, a significant benefit was seen in the change in total PDQ-39 score from baseline 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).<sup>4</sup> This manufacturer-funded moderate quality trial had a high overall attrition of 11.2% with adequate randomization and blinding.<sup>4</sup> Additionally, all of the treatment centers were located in India, Romania, or Italy, which limits applicability to the Oregon Medicaid population.<sup>4</sup>

The SETTLE study was a double-blinded, parallel-group, placebo-controlled 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.<sup>3</sup> At day 14, 90.9% of the safinamide group and 94.1% in the placebo group were prescribed the 100 mg/day target dose.<sup>3</sup> Inclusion criteria were similar to Study-016.<sup>3</sup> The average age of the patients was 61.9 years, 60.9% were male, and 67.6% of the patients were white.<sup>3</sup> All patients took concomitant levodopa with a mean dose of 776.6 mg/day, the mean Hoehn & Yahr stage was 2.5, and the mean UPDRS part III score was 22.9.<sup>3</sup> At week 24, there was a significant benefit in the primary

endpoint of change from baseline to week 24 in mean daily “on” time without troublesome dyskinesia 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).<sup>3</sup> There was also a significant benefit seen in the secondary endpoint of change from baseline to week 24 in “off” time with safinamide (-1.56 h/d; mean difference vs. placebo -1.03h; 95% CI -1.40 to -0.67;  $p < 0.001$ ) compared to placebo (-0.54 h/d).<sup>3</sup> In terms of quality of life, a significant benefit was also seen in the PDQ-39 summary index score with safinamide compared to placebo (-3.17 vs. -0.68 points, respectively; MD -2.49; 95% CI -3.98 to -0.68;  $p = 0.006$ ).<sup>3</sup> This manufacturer-funded moderate quality trial had high overall attrition of 11.5% with adequate randomization and blinding.<sup>3</sup> Only 18% of patients were from North America, which may limit applicability to the Oregon Medicaid population.<sup>3</sup>

Study-018 was an 18 month multicenter, randomized, double-blind, placebo-controlled, parallel-group extension study of Study-016.<sup>33</sup> Included patients completed Study-016, were treatment compliant and willing to continue, or had discontinued from Study-016 but completed efficacy evaluations at weeks 12 and 24.<sup>33</sup> Patients continued in the same treatment group that they had been randomized to in Study-016.<sup>33</sup> At week 78, there was not significant benefit 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 -0.59h; 95% CI -1.40 to 0.21;  $p = 0.1469$ ) or safinamide 50 mg/day (mean difference -0.51h; 95% CI -1.32 to 0.29;  $p = 0.2125$ ) compared to placebo.<sup>33</sup> However, there was a 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 0.83h; 95% CI 0.39 to 1.27;  $p = 0.0002$ ) and safinamide 50 mg/day (mean difference 0.67h; 95% CI 0.23 to 1.11;  $p = 0.0031$ ) compared to placebo.<sup>33</sup> This low quality manufacturer-funded trial had 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.<sup>33</sup>

These three studies (Study-016, SETTLE, and Study-018) provide data of benefit in the PD population as an adjunct to levodopa treatment in patients experiencing “off” episodes.<sup>3,4,32</sup> Improvement was seen in motor complications through total daily “on” time with no or non-troublesome dyskinesia.<sup>3,4,32</sup> Quality of life as measured by PDQ-39 scores was also improved.<sup>3,4</sup>

In February 2017, an evidence summary on PD with motor fluctuations with a focus on safinamide was published by NICE.<sup>20</sup> This review summarized evidence from Study-016, SETTLE, and Study-018.<sup>3,4,20,33</sup> No recommendations were made but NICE guidance on Parkinson’s disease (detailed previously in this review) in adults was referenced.<sup>1,20</sup>

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

Three phase 3 studies were completed studying safinamide as an add-on therapy to dopamine agonists, which is an indication which was ultimately not approved by the FDA.<sup>7-10</sup> These trials are Study-015, Study-017, and MOTION.<sup>7-9</sup> The primary outcome studied in Study-015 was change in UPDRS part III (motor examination) total score from baseline to week 24.<sup>8</sup> There was no change in the primary outcome for the comparison of safinamide 200 mg 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 versus placebo (-6.0 vs. -3.6, respectively; 95% CI -3.7 to -0.1;  $p = 0.0419$ ).<sup>8</sup> However, the FDA clinical review 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.<sup>8,10</sup> Therefore, statistical testing could not be formally conducted for the low dose as the high dose did not show statistically significant results.<sup>8,10</sup>

Study-017 was a 12 month randomized, double-blind, placebo-controlled extension study of Study-015.<sup>7</sup> 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.<sup>7</sup> There was no benefit seen in the primary endpoint with the safinamide groups (pooled doses) versus placebo (559 days vs. 466 days, respectively;  $p = 0.3342$ ).<sup>7</sup> 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).<sup>7</sup> 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 (LS difference vs. placebo -0.65; p=0.259) or 100 mg/day versus placebo (LS difference vs. placebo -1.04; p=0.073).<sup>9,10</sup>

Based on these 3 trials, the FDA determined that there was not sufficient evidence to support approval of safinamide in the early PD population.<sup>10</sup>

**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 (17%), fall (6%), nausea (6%), and insomnia (4%).<sup>3,4,32</sup>

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.<sup>4</sup> No specific pattern of SAEs was determined.<sup>4</sup> In SETTLE, 9.5% (n=26) and 6.6% (n=18) of safinamide- and placebo-treated patients experienced SAEs.<sup>3</sup> SAEs which occurred in more than one safinamide-treated patient included breast cancer (n=2) and visual hallucinations (n=2).<sup>3</sup>

Dyskinesia was the most commonly reported adverse event in both Study-016 and SETTLE.<sup>3,4</sup> 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.<sup>4</sup> However, severe dyskinesia was only reported in 0.9%, 1.8%, and 2.3% of those same groups.<sup>4</sup> 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.<sup>3</sup>

In terms of long-term extension trial data, the percent of patients experiencing newly emergent TEAEs in Study-018 separate from Study-016 for safinamide 100 mg/day, safinamide 50 mg/day, and placebo groups were 78.3%, 76.7%, and 85.1%, respectively.<sup>33</sup> During the two year treatment period of Study-016 and Study-018 combined, worsening of PD and dyskinesia were the most frequent TEAEs.<sup>33</sup> Worsening of PD was reported in 22.2%, 23.9%, and 24.0% of patients treated with safinamide 50 mg/day, safinamide 100 mg/day, and placebo, respectively. Dyskinesia was reported in 31.2%, 27.8%, and 21.7% of those groups, respectively.<sup>33</sup> Discontinuation due to TEAEs occurred in 5.3%, 6.7%, and 5.7% of the safinamide 50 mg/day, safinamide 100 mg/day, and placebo groups.<sup>33</sup>

Per package labeling, safinamide is contraindicated in patients with concomitant use of other monoamine oxidase inhibitors, opioids, and dextromethorphan as well as in patients with a history of hypersensitivity to safinamide or in severe hepatic impairment (Child-Pugh C).<sup>32</sup>

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

**Table 1. Pharmacology and Pharmacokinetic Properties.**<sup>32</sup>

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 2. 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 <sup>4</sup>  STUDY-016  Phase 3, randomized, MC, DB, PC, PG	1. Safinamide 100 mg/d  2. Safinamide 50 mg/d  3. Placebo  4 phases: • 10d screening period • 4w L-dopa stabilization period • 24w treatment period • Optional 1w taper period  Randomized 1:1:1	<u>Demographics:</u> -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 -Mean UPDRS-III: 28.1  <u>Key Inclusion Criteria:</u> -30-80 y of age -idiopathic PD $\geq$ 3 y -Hoehn & Yahr stage I-IV during “off”	<u>ITT:</u> Total: 669 1. 224 2. 223 3. 222  <u>Attrition:</u> Total: 11.2% 1. 29 (12.9%) 2. 21 (9.4%) 3. 25 (11.3%)	<u>Primary Endpoint:</u> Change in mean daily total “on” time with no or non-troublesome dyskinesia at week 24: 1. 1.36 $\pm$ 2.625 h 2. 1.37 $\pm$ 2.745 h 3. 0.97 $\pm$ 2.375 h  <u>1 vs. 3: LS mean change: 0.55h (95% CI, 0.07-0.94); P=0.0223</u> <u>2 vs. 3: LS mean change: 0.51h (95% CI, 0.12-0.99); P=0.0130</u>  <u>Secondary Endpoints:</u> (reported as change from baseline to week 24) Change in total daily “off” time: 1. -1.3h 2. -1.3h 3. -0.7h <u>1 vs. 3: LS mean difference: -0.6h (95% CI, -1.0 to -0.2); P=0.0034</u> <u>2 vs. 3: LS mean difference: -0.6h (95% CI, -0.9 to -0.2); P=0.0043</u>  Change in UPDRS Part III (motor) scores during “on”: 1. -6.9 2. -6.1	NA for all	<u>Study drug-related AE:</u> 1. 67 (29.9%) 2. 69 (30.9%) 3. 51 (23.0%) P=0.1395 RR & 95% CI NR  <u>Serious AE:</u> 1. 22 (9.8%) 2. 8 (3.6%) 3. 18 (8.1%) P=0.0286 RR & 95% CI NR  <u>DC due to AE:</u> 1. 14 (6.3%) 2. 11 (4.9%) 3. 12 (5.4%) P=0.8497 RR & 95% CI NR  <u>Dyskinesia:</u>	NA NA  NA 4.5% /23  NA NA  NA	<b>Risk of Bias (low/high/unclear):</b> <u>Selection Bias:</u> Low. Randomization by computer-generated randomization schedule, administered by central IVRS. Baseline characteristics balanced. <u>Performance Bias:</u> Low. Safinamide and placebo identical in appearance. Protocol approved in all countries studied. <u>Detection Bias:</u> Low. Investigators, patients, and caregivers blinded to treatment. <u>Attrition Bias:</u> High. Overall attrition >10%. MMRM analysis utilized for primary endpoint with no imputations for missing data. ITT analysis used. <u>Reporting Bias:</u> Unclear. All primary and secondary efficacy endpoints reported, although study protocol not available. Funded by Newron and Merck Serono.

		<p>-motor fluctuations (&gt;1.5 h "off" time/d)</p> <p><u>Key Exclusion Criteria:</u>  -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</p>		<p>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</p> <p>Change in UPDRS Part II (activities of daily living) scores during "on":  1. -2.2  2. -1.7  3. -1.2  1 vs. 3: -1.0h (95% CI, -1.7 to -0.3); P=0.0060  2 vs. 3: -0.5h (95% CI, -1.2 to 0.2); P=0.1253</p> <p>Change in "off" time following first morning L-dopa dose:  1. -1.2h  2. -1.1h  3. -0.6h  1 vs. 3: -0.6h (95% CI, -1.0 to -0.2); P=0.0011  2 vs. 3: -0.5h (95% CI, -0.9 to -0.2); P=0.0031</p> <p>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</p>		<p>1. 41 (18.3%)  2. 47 (21.1%)  3. 28 (12.6%)  RR, 95% CI, &amp; p-value NR</p> <p><u>Severe dyskinesia:</u>  1. 1.8%  2. 0.9%  3. 2.3%  RR, 95% CI, &amp; p-value NR</p>	<p>NA</p> <p>NA</p> <p>NA</p>	<p><b>Applicability:</b>  <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> An active comparator would have been a more meaningful comparison than placebo.  <u>Outcomes:</u> Outcomes appropriate for condition.  <u>Setting:</u> 52 treatment centers in India (35), Romania (10), and Italy (7). May limit applicability to the U.S. population.</p>
<p>2. Schapira, et al<sup>3</sup></p> <p>SETTLE</p> <p>DB, PG, PC, phase 3 trial</p>	<p>1. Safinamide 50 mg/d days 1-13, then 100 mg/d starting on day 14 if no tolerability issues</p> <p>2. Placebo daily</p> <p>24 weeks</p> <p>Randomized 1:1</p>	<p><u>Demographics:</u>  -Age: 61.9 y  -Male: 60.9%  -White: 67.6%  -North America: 18.6%  -Western Europe: 39.9%  -Mean Hoehn &amp; 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</p> <p><u>Key Inclusion Criteria:</u>  -30-80 y of age</p>	<p><u>ITT:</u>  Total: 549  1. 274  2. 275</p> <p><u>Attrition:</u>  Total: 63 (11.5%)  1. 29 (10.6%)  2. 34 (12.4%)</p>	<p><u>Primary Endpoint:</u>  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&lt;0.001</p> <p><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&lt;0.001</p> <p>Change in UPDRS Part III score from baseline to week 24:  1. -3.43</p>	<p>NA</p> <p>NA</p> <p>NA</p>	<p><u>Study drug-related AE:</u>  1. 78 (28.5%)  2. 76 (27.6%)</p> <p><u>Serious AE:</u>  1. 18 (6.6%)  2. 26 (9.5%)</p> <p><u>Study drug-related serious AE:</u>  1. 3 (1.1%)  2. 6 (2.2%)</p> <p><u>DC due to AE:</u>  1. 12 (4.4%)  2. 10 (3.6%)</p>	<p>NA</p> <p>NA</p> <p>NA</p> <p>NA</p>	<p><b>Risk of Bias (low/high/unclear):</b>  <u>Selection Bias:</u> Low.  Randomization by and allocation via computerized central IVRS. Baseline characteristics balanced.  <u>Performance Bias:</u> Low. Placebo was provided as matching tablets 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 &gt;10%. LOCF approach to missing data utilized for a chronic, deteriorating condition. ITT analysis.  <u>Reporting Bias:</u> Unclear. Protocol available. All primary and</p>

		<p>-idiopathic PD <math>\geq</math>3 y -Hoehn &amp; Yahr stage I-IV during "off" -motor fluctuations (&gt;1.5 h "off" time/d) -L-dopa responsive and on stable regimen x4w</p> <p><b>Key Exclusion Criteria:</b> -severe, disabling peak-dose or biphasic dyskinesia -wide or unpredictable symptom fluctuations -current diagnosis of a clinically significant medical condition other than PD</p>		<p>2. -1.83 LS mean difference: -1.82 (95% CI, -3.01 to -0.62); P=0.003</p> <p>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</p> <p>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&lt;0.001</p> <p>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</p>	NA	<p><b>Deaths:</b> 1. 1 (0.4%) 2. 2 (0.7%)</p> <p><b>Dyskinesia:</b> 1. 40 (14.6%) 2. 15 (5.5%)</p> <p>RR, 95% CI, &amp; p-value NR</p>	NA	<p>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.</p> <p><b>Applicability:</b> <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> An active 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.</p>
3.Borghain, et al <sup>33</sup>	<p>Same as Study-016</p> <p>1. safinamide 100 mg/d</p> <p>2. safinamide 50 mg/d</p> <p>3. placebo</p> <p>Patients continued in same group they were randomized to in Study-016.</p>	<p><b>Demographics:</b> -Age: 59.9 y -Male: 71.8% -Asian: 80.6% -White: 19.4% -Mean Hoehn &amp; Yahr stage: 2.8 -Concomitant L-dopa: 100% -Mean L-dopa dose: 604.85 mg -Concomitant dopamine agonist: 60.8% -Concomitant anticholinergic: 37.1% -Mean daily total "on" time with no or non-</p>	<p><b>ITT:</b> Total: 544 1. 180 2. 189 3. 175</p> <p><b>Attrition:</b> Total: 104 (19.1%) 1. 30 (16.7%) 2. 41 (21.7%) 3. 33 (18.9%)</p>	<p><b>Primary Endpoint:</b> LS mean change from baseline (Study-016 start) to week 78 of total score of the DRS during "on" time: 1. -0.28 2. -0.19 3. +0.32</p> <p>1 vs. 3: LS mean difference: -0.59 (95% CI, -1.40 to 0.21); P=0.1469 2 vs. 3: LS mean difference: -0.51 (95% CI, -1.32 to 0.29); P=0.2125</p> <p><b>Secondary Endpoints:</b> LS mean change from baseline to week 78 in total daily "on" time without troublesome dyskinesia: 1. 1.18h 2. 1.01h 3. 0.34h</p>	NA NA	<p><b>Newly emergent TEAE during Study-018:</b> 1. 141 (78.3%) 2. 145 (76.7%) 3. 149 (85.1%)</p> <p><b>Any serious TEAE:</b> 1. 34 (18.9%) 2. 32 (16.9%) 3. 28 (16.0%)</p> <p><b>DC due to TEAEs:</b> 1. 12 (6.7%) 2. 10 (5.3%)</p>	NA NA NA NA	<p><b>Risk of Bias (low/high/unclear):</b> <u>Selection Bias:</u> Low. Randomization in Study-016 by computer-generated randomization schedule, administered by central IVRS. Baseline characteristics balanced. <u>Performance Bias:</u> Unclear. Safinamide and placebo identical in appearance in Study 016, but no description of if matching placebo in Study 018. Protocol approved by all appropriate independent ethics committees and regulatory authorities. <u>Detection Bias:</u> High. Double-blind but unclear which groups blinded. Did not discuss blinding</p>

		<p>troublesome dyskinesia: 9.4 h -Mean UPDRS-III: 28.1</p> <p><u>Key Inclusion Criteria:</u> -See Study-016 -Patients were included in Study-018 if they completed Study-016, were treatment compliant and willing to continue, or if they had discontinued from Study 016 but had completed scheduled efficacy evaluations at weeks 12 and 24.</p> <p><u>Key Exclusion Criteria:</u> -See Study-016 -Patients from Study-016 were excluded if they had clinically significant AEs or shown clinically significant deterioration in motor symptoms during Study 016</p>		<p>1 vs. 3: 0.84h (95% CI, 0.39 to 1.27); P=0.0002 2 vs. 3: 0.67h (95% CI, 0.23 to 1.11); P=0.0031</p> <p>Outcomes for other secondary endpoints NR. Only differences versus placebo and p-values reported.</p>	<p>NA NA</p>	<p>3. 10 (5.7%)</p> <p><u>Worsening of PD:</u> 1. 43 (23.9%) 2. 42 (22.2%) 3. 42 (24.0%)</p> <p><u>Dyskinesia:</u> 1. 50 (27.8%) 2. 59 (31.2%) 3. 38 (21.7%)</p> <p>RR, 95% CI, &amp; p-value NR</p>	<p>NA NA</p> <p>NA NA</p>	<p>of patients who had discontinued Study 016.</p> <p><u>Attrition Bias:</u> High. Overall attrition ~20%. ITT analysis used.</p> <p><u>Reporting Bias:</u> High. Outcomes for most secondary endpoints NR; only differences versus placebo and p-values reported. Emphasis of ad-hoc analyses with non-significant primary endpoint. Funded by Newron and Merck Serono.</p> <p><b>Applicability:</b> <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> An active comparator would have been a more meaningful comparison. <u>Outcomes:</u> Outcomes appropriate for condition. <u>Setting:</u> 52 treatment centers in India, Romania, and Italy. May limit applicability to the U.S. population.</p>
<p><b>Abbreviations [alphabetical order]:</b> 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; PC = placebo controlled; PD = Parkinson's disease; PDQ-39 = Parkinson's Disease Questionnaire; PG = parallel-group; PP = per protocol; TEAE = treatment-emergent adverse event; w = week; Y = years</p>								

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**Appendix 1: Current Preferred Drug List**

<b>PDL</b>	<b>Generic</b>	<b>Brand</b>	<b>Route</b>	<b>Form</b>
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

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## 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

#### 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](http://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

Appendix 4: Prior Authorization Criteria

## Anti-Parkinson's Agents

**Goals:**

- Promote preferred drugs for Parkinson's disease.
- Restrict use for non-funded conditions like (e.g., restless leg syndrome).

**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](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://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?	<b>Yes:</b> Go to #5	<b>No:</b> Go to #3
3. Is the diagnosis Restless Leg Syndrome?	<b>Yes:</b> Pass to RPh. Deny; not funded by the OHP.	<b>No:</b> Go to #4
4. RPh only: All other indications need to be evaluated to determine if treatment is for a funded condition.	<b>Funded:</b> Go to #5	<b>Not Funded:</b> Deny; not funded by the OHP.

## Approval Criteria

5. 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:** Approve for the shorter of 1 year or length of prescription.

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

Appendix 5: Proposed Prior Authorization Criteria for Safinamide

**Safinamide**

**Goal(s):**

- To limit utilization of safinamide to FDA-approved indications.

**Length of Authorization:**

Up to 12 months

**Requires PA:**

- Safinamide (Xadago®)

**Covered Alternatives:**

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; not funded by the OHP.
3. Will the prescriber consider a change to a preferred product?  Message: <ul style="list-style-type: none"> <li>Preferred products do not require a PA.</li> <li>Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy &amp; Therapeutics Committee.</li> </ul>	<b>Yes:</b> Inform prescriber of covered alternatives in class.	<b>No:</b> Go to #4
4. Does the patient have a diagnosis of Parkinson’s disease and experiences “off” episodes?	<b>Yes:</b> Go to #5	<b>No:</b> Pass to RPh. Deny; medical appropriateness.

## Approval Criteria

5. Is the patient currently taking levodopa/carbidopa?

**Yes:** Approve for up to 12 months.

**No:** Pass to RPh. Deny; medical appropriateness.

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*P&T/DUR Review: 3/18 (JP)  
Implementation: TBD*

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