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Drug Class Update with New Drug Evaluation: Parkinson's Disease Drugs

Date of Review: October 2020

Date of Last Review: March 2018
Dates of Literature Search: 01/01/2018 - 01/01/2020
Brand Name (Manufacturer): NOURIANZ (Kyowa)
OGENTYS (Neurocrine)
KYNMOBI (Sunovion)

Generic Name: istradefylline
opicapone
apomorphine sublingual

Dossier Received: yes

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

Purpose for Class Update:
Review the evidence for new drugs recently approved as adjunctive treatment to levodopa therapy in adults with Parkinson's disease. Review updated evidence for the drug class in a broader context to validate current Oregon Health Plan (OHP) Fee-for-Service (FFS) Preferred Drug List (PDL) and current clinical Prior Authorization (PA) criteria.

Research Questions:
1. Is there new comparative evidence that drugs indicated for treatment of Parkinson's disease (PD) differ in efficacy or effectiveness at improving symptoms, quality of life or in stabilizing disease progression in adults with PD?
2. Is there new comparative evidence that drugs indicated for treatment of PD differ in serious adverse events or tolerability when used to treat adults with PD?
3. Are there specific subpopulations based on demographic characteristics (e.g., age, gender, race, disease severity or longevity, disease subtype, or concomitant therapies) for which one anti-PD drug is better tolerated or more effective than other available drugs used to manage PD?

Conclusions:
- Three new high-quality systematic reviews of drugs indicated for treatment of PD and one new drug approval for adjunctive treatment of PD were identified since the last drug class review. No new high-quality clinical practice guidelines, safety alerts or new drug formulations in this drug class were found.
- One systematic review provided low quality evidence that monoamine oxidase B inhibitors (MAOBIs) are effective compared to placebo, both when given as monotherapy and in combination with levodopa therapy.[1] No statistically significant differences in relative effectiveness between rasagiline, safinamide and selegiline were found based on achievement of 20% score reduction in the total Unified Parkinson's Disease Rating Scale (UPDRS) score (relative risk [RR]

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1.560 (95% CI, 1.409 to 1.734), RR 1.449 (95% CI, 0.873 to 2.413) and RR 1.532 (95% CI, 1.337 to 1.757), respectively).[1] Rasagiline, safinamide and selegiline were also effective compared to placebo when these drugs were used as adjunctive therapy with levodopa therapy (RR 1.573 (95% CI, 1.369 to 1.803), RR 1.178 (95% CI, 1.031 to 1.350) and RR 2.307 (95% CI, 1.802 to 2.936), respectively).[1] No increased risk for serious adverse events with a MAOBI compared to placebo or placebo plus levodopa therapy were found.[1]

- The incidences of adverse effects between immediate-release (IR) and extended-release (ER) formulations of pramipexole, a dopamine agonist, were systematically reviewed and found to be similar.[2]
- One multi-centered randomized controlled trial (RCT) provided moderate quality evidence that delaying initiation of levodopa therapy in patients with newly diagnosed PD by 40 weeks does not impact long-term functioning based on change in the total UPDRS score at 80 weeks (mean difference 1.0 (95% CI, -1.5 to 3.5; p=0.44).[3]

Istradefylline:

- Istradefylline was studied as adjunctive treatment to levodopa therapy in patients with advanced PD in 8 RCTs. Five RCTs[4-8] found istradefylline decreased daily "off" time in patients and 3 RCTs did not, including an active-controlled study that found benefit with entacapone but not istradefylline.[9-11] The FDA approved istradefylline based on the positive findings of 4 of the 8 RCTs.[4,6-8]
- The primary efficacy endpoint in these RCTs was the change from baseline in daily awake percentage of "off" time, or the change from baseline in total daily "off" time based on 24-hour "on/off" diaries completed by patients, over 12 weeks. These studies provide low quality evidence of benefit for istradefylline over placebo in reduction of "off" time by about 0.7 to 0.9 hours per day, which correlated to a relative reduction of about 15% from "off" time experienced at baseline.[12]
- Of the 4 trials the FDA considered for approval, 2 trials found a 2-point benefit with the 40 mg dose in the UPDRS part 3 "on" state[7,8] and one trial found a 1.7-point benefit in the UPDRS part 2 "off" state with the 40 mg dose.[8] Other UPDRS sections did not improve with istradefylline, including Part 1; Part 2 "on" and Part 4. Total UPDRS scores also did not differ between istradefylline and placebo.[4] None of the clinical trials found clinically meaningful differences between istradefylline and placebo in improvement of UPDRS scores over 12 weeks of treatment.
- The most frequent adverse effects observed in clinical trials 5% or greater frequency than placebo were dyskinesia, dizziness, constipation, nausea, hallucinations and insomnia.[12] Overall, the frequency of serious adverse events was low and similar across all treatment groups.

Opicapone:

- The efficacy and safety of opicapone was established in two identical double-blind, randomized, placebo-controlled trials in patients with idiopathic PD and motor fluctuations already treated with levodopa therapy. The primary efficacy endpoint for both studies was the total reduction in daily "off" time assessed using 24-hour patient diaries in which patients recorded their status at 30-minute intervals for the 3 consecutive days before clinic visit 7 (week 14-15).[13,14] The studies provide low quality evidence that opicapone 50 mg daily reduced "off" time by 54-61 minutes per day versus placebo (study 301: mean difference [MD] = -60.8 min [95% CI, -97.2 to -24.4]; and study 302: MD = -54.3 min [95% CI, -96.2 to -12.4]).[13,14] None of the key secondary endpoints, which included change in total UPDRS, change in the Parkinson's Disease Sleep Scale (PDSS), change in Non-motor Symptoms Scale (NMSS), and the Parkinson's Disease Questionnaire (PDQ-39) questionnaire, were found to differ between opicapone and placebo. Dyskinesia was the most common adverse event reported with opicapone, and the most common adverse event leading to early study discontinuation.[13,14]

Apormorphine, sublingual (SL):

- The efficacy and safety of apomorphine SL was established in a single randomized, placebo-controlled trial.[15] The study included an open-label apomorphine SL titration phase and a 12-week double-blind, placebo-controlled maintenance phase.[15] In the titration phase, all patients were titrated to a tolerable dose of apomorphine SL (maximum dose 35 mg) that achieved a full "on" response. Patients who met criteria were randomized to apomorphine SL or placebo in

the maintenance phase. The primary endpoint for the study was the mean change from pre-dose to 30 minutes post-dose in the MDS-UPDRS Part 3 (motor examination).[15] The key secondary endpoint was the percentage of patients with a patient-rated full "on" response within 30 minutes at the week 12.[15]

- The study provides low quality evidence that apomorphine SL provided greater reduction in the MDS-UPDRS part 3 score at week 12 than placebo (-11.1; 95% CI, -14.0 to -8.2 vs. -3.5; 95% CI, -6.1 to -0.9, respectively) by a least squares mean difference of -7.6 (95% CI, -11.5 to -3.7).[15] The response rate for a full "on" response within 30 minutes at the week 12 visit was also greater in patients treated with apomorphine SL than in those treated with placebo (35% vs. 16%, respectively; OR 2.81; 95% CI, 1.04 to 7.64).[15] Treatment-emergent adverse events led to early study discontinuation in 28% of patients treated with apomorphine SL and in 9% of those treated with placebo.[15] Oropharyngeal adverse events occurred in 31% of patients treated with apomorphine SL and were the most common type of adverse event that led to study discontinuation in the double-blind maintenance phase of the trial (17%).[15]

Recommendations:

- Designate istradefylline, opicapone and apomorphine SL as a non-preferred drug on the OHP Practitioner-Managed Prescription Drug Plan (PMPDP).
- Update clinical PA criteria to ensure istradefylline, opicapone and apomorphine SL are used as an adjunct to levodopa therapy in patients with PD (see **Appendix 6**).
- Review comparative drug costs in the executive session.

Summary of Prior Reviews and Current Policy

- The current OHP FFS PDL includes first-line treatment options for PD, including several formulations of levodopa/carbidopa, and adjunctive therapy such as dopamine agonists (pramipexole), MAOBI (selegiline), catechol-O-methyltransferase inhibitors (COMTI) (entacapone, tolcapone), and anticholinergic agents (benztropine, trihexyphenidyl).
- Clinical PA criteria limits these agents to funded conditions under the OHP and requires current use of levodopa/carbidopa in patients prescribed safinamide.
- Current guidance from the National Institute for Health and Care Excellence (NICE) supports the current PDL and clinical PA criteria.[16]
- From the previous drug class update[17]:
    - No new safety alerts or comparative evidence of anti-PD drugs were identified.
    - Extended-release amantadine (Gocovri™) was approved by the FDA for the treatment of dyskinesia in patients with PD receiving levodopa-based therapy based on low quality evidence from 2 placebo-controlled studies.
    - Low quality of evidence demonstrated that safinamide, when used as an adjunct to levodopa therapy, may improve quality of life, increase total daily "on" time, and decrease "off" time in patients in later stages of PD relative to placebo.

Background:

Parkinson's disease is an incurable, progressive neurodegenerative disorder caused by the death of dopamine-secreting neurons in the sunbstantia nigra. The resulting dopamine deficiency within the basal ganglia slowly leads to a movement disorder characterized by "parkinsonian" motor symptoms, including bradykinesia, rigidity and resting tremor.[18] However, non-specific non-motor symptoms such as olfactory dysfunction, constipation, sleep disorders, and depression may precede motor symptoms by several years.[18] As PD advances, patients develop motor fluctuations (alterations between response to anti-PD drug therapy and reemergance of symptoms as the benefit of drug therapy wears off) and non-motor complications (e.g., autonomic, psychiatric and cognitive impairment).

Parkinson's disease is the most common neurodegenerative disorder after Alzheimer's disease.[18] Parkinson's disease was earlier thought to be caused primarily by environmental factors, but research continues to reveal that PD develops from a complicated interplay of genetic and environmental factors.[18] Age is the greatest risk factor for the development of PD; other established risk factors include gender (male-to-female ratio of 1.5:1) and ethnicity (highest in people of Hispanic descent, followed by non-Hispanic Whites, Asians and Blacks).[18] The typical age of onset is around 60 years, but prevalence and incidence increase almost exponentially with age and peak after 80 years of age.[18,19] The prevalence of PD is about 1 million people in North America, or about 1% of the population older than 60 years.[19]

The mainstay of PD management is symptomatic treatment with drugs that increase dopamine concentrations or directly stimulate dopamine receptors. However, PD will ultimately cause progressive disability despite treatments that may be initially effective. As PD advances, nondopaminergic regions of the brain become involved and this results in treatment-resistant motor and nonmotor symptoms.[19] There are no established disease-modifying or neuroprotective therapies for PD; therefore, treatment does not need to begin at time of diagnosis but, rather, when patients experience functional impairment or social embarrassment from their symptoms.[19] The primary goal of treatment is to improve function and quality of life for as many years as possible.

The most effective treatment for the disease is oral levodopa (dopamine's lipophilic precursor) in combination with a dopa decarboxylase inhibitor (e.g., carbidopa) to reduce the peripheral degradation of levodopa. Multiple large trials have shown levodopa provides the greatest symptomatic benefit for PD and is associated with less freezing, somnolence, edema, hallucinations, and risk of impulse disorders than dopamine agonists.[19] However, long-term treatment with levodopa and a dopa decarboxylase inhibitor (hereafter referred to as levodopa therapy) is complicated by the development of motor fluctuations and dyskinesia. Motor fluctuations are characterized by a cycle in which patients have a long period of drug responsiveness ("on" periods) followed by a return of parkinsonian symptoms ("off" episode) before the benefit from the next subsequent dose takes effect. These motor fluctuations are largely due to the short half-life of levodopa. Off episodes can manifest as "parkinsonian" motor symptoms. Dopamine agonists, however, are associated with less dopaminergic complications like dyskinesia, which can be a major factor when treatment is initiated in younger patients with PD who are at higher risk for dyskinesia.[19] Other adjunctive therapies include MAOBIs and COMTIs. Evidence supporting amantadine for treatment of PD is insufficient; however, the drug is believed to be effective when used in clinical practice.[19]

Three new anti-PD agents were recently approved by the FDA to manage "off" episodes. Istradefylline was approved by the FDA in August 2019 for adjunctive treatment to levodopa therapy in patients with advanced PD experiencing "off" episodes.[12] Istradefylline is a new molecular entity, and the first adenosine A2A receptor antagonist approved for the treatment of motor fluctuations in advanced PD. Opicapone was approved by the FDA in April 2020 for adjunctive treatment to levodopa therapy in patients with PD experiencing "off" episodes.[20,21] Opicapone is a COMTI similar to entacapone and tolcapone. Entacapone is the most commonly used COMTI for the management of "off" episodes, but it needs to be given concomitantly with each levodopa dose; tolcapone is limited by hepatotoxicity and continuous monitoring of liver function.[22] Until recently, two treatment options are available for on-demand, "rescue" management of "off" episodes: subcutaneous apomorphine, a non-ergoline dopamine agonist, and an inhaled dry powder formulation of levodopa. However, an apomorphine sublingual film formulation was approved by the FDA in May 2020 to address the practical limitations with the SC apomorphine.[15,23]

When motor fluctuations are present in advanced PD, strategies to reduce "off" time include increasing the dose of dopaminergic medication, adding another dopaminergic medication (e.g., dopamine agonist), dividing the levodopa dose into smaller but more frequent doses, or adding a COMTI or MAOBI to inhibit the breakdown of levodopa and dopamine and prolong their effect.[19] However, few trials have compared these different strategies. As PD progresses, patients on levodopa therapy often add one of these classes of drug; and as PD advances further, patients may eventually take drugs from 2 or 3 of these classes, in addition to levodopa.[12] The overall benefit of these adjunctive treatments relative to placebo in decreasing total "off" time ranges from about 0.5 to 2 hours.[12] None of

these adjunctive drugs have been shown to be superior to others for treating "off" time.[12] In practice, it is important to regularly re-evaluate the ongoing efficacy and adverse effects of these adjunctive drugs so treatment can be tailored to the patient's needs.

In an evaluation of paid and denied claims from 7/1/19 to 9/30/19, there were approximately 370 OHP FFS patients prescribed therapies within this drug class. About 64% of prescribed therapy was for preferred agents (primarily benztropine and pramipexole). Of note, only 25 patients (7%) had claims for levodopa therapy. Amantadine and ropinirole were the most commonly prescribed non-preferred products. Of the patients prescribed a non-preferred drug, 47% had a subsequent PA request approved and 5% of patients switched to a preferred drug. Of the patients with no subsequent paid PD therapy, 37% were enrolled in a coordinated care organization, lost eligibility or had other insurance which may have paid for their medication. Only 5% of patients had a PA denied and 5% of patients had no PA requested by the prescribing provider.

The PD-specific instruments commonly used in clinical trials to evaluate disease progression and treatment efficacy include the Hoehn and Yahr (HY) staging system, the UPDRS: Parts I-IV, and the Parkinson's Disease Questionnaire (PDQ-39).

Hoehn and Yahr staging was originally designed to be a descriptive staging scale that provided a general estimate of clinical function in PD, combining functional deficits (disability) and objective signs (impairment). The 5-point (1 to 5) HY scale is based on the 2-fold concept that the severity of overall parkinsonian dysfunction relates to bilateral motor involvement and compromised balance and gait. Increasing parkinsonian motor impairment is scaled from unilateral (Stage 1) to bilateral disease without balance difficulties (Stage 2), to the presence of postural instability (Stage 3), loss of physical independence (Stage 4), and being wheelchair- or bed-dependent (Stage 5).[24]

The UPDRS scale is a rating tool used to gauge the course of PD in patients.[25] The UPDRS continues to be used in research to estimate treatment effects for PD. The UPDRS scale consists of the following 4 sections: 1) non-motor experiences of daily living (evaluation of mentation, behavior and mood); 2) motor experiences of daily living (e.g., speech, swallowing, handwriting, falling, walking, etc.); 3) motor examination (by clinician); and 4) motor complications.[25] Each item in each section is ranked on a 5-point scale (0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe) and higher scores indicate more severe PD; the total cumulative UPDRS score will range from 0 (no disability) to 199 (total disability). The UPDRS cut-off points between mild/moderate and moderate/severe levels for each section are estimated to be: Part 1: 10/11 and 21/22; Part 2: 12/13 and 29/30; Part 3: 32/33 and 58/59; and Part 4: 4/5 and 12/13.[26] The minimally important clinical difference (MCID) thresholds for components of the UPDRS have been estimated based on clinical trials.[27,28] The MCID for improvement in Part 2 of the UPDRS is about -2 points, and the MCID for Part 3 is about -6 points in both early and advanced PD patients.[27] An updated UPDRS by the Movement Disorders Society (MDS) in 2008 provided clarity to some ambiguities of the original scale with slight modifications.[25] The MCID thresholds for Part 3 MDS-UPDRS motor examination score have also been examined, and are estimated to be -3.25 points for observing minimal, but clinically relevant improvement and 4.63 points for observing minimal, but clinically relevant worsening.[28]

The PDQ-39 is a PD-specific quality of life questionnaire.[29,30] The instrument has been tested for reliability and validity and is now widely used in clinical trials and practice.[30] The PDQ-39 assesses how often people with PD experience difficulties across 8 dimensions of health: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and body discomfort.[29,30] Dimension scores are coded on a scale of 0 (perfect health as assessed by the measure) to 100 (worst health as assessed by the measure).[30] The MCID thresholds for PDQ-39 total index (100-point scale) are estimated to be -4.72 and +4.22 for detecting minimal clinically important improvement and worsening, respectively.[31]

Non-motor symptoms in PD are common and can significantly reduce quality of life. The Non-motor Symptoms Scale (NMSS) addresses non-motor symptoms, and consists of 30 questions, covering 9 dimensions (cardiovascular, sleep/fatigue, mood/cognition, perceptual problems, attention/memory, gastrointestinal, urinary, sexual function, and miscellany), whereby each item is scored based on a multiple of severity (from 0 to 3) and frequency scores (from 1 to 4).[32] The NMSS is rated by the healthcare provider and obtained through interview. The NMSS total score is calculated by adding all domain scores (0-360), and lower scores mean less disability.[32] An MCID has not been recognized for the NMSS.

The Parkinson's disease Sleep Scale (PDSS) is a specific scale for the assessment of sleep disturbances in subjects with PD.[33] The PDSS is a visual analogue scale addressing 15 commonly reported symptoms associated with sleep disturbance.[33] Items of the PDSS address the following: overall quality of night's sleep (item 1); sleep onset and maintenance insomnia (items 2 and 3); nocturnal restlessness (items 4 and 5); nocturnal psychosis (items 6 and 7); nocturia (items 8 and 9); nocturnal motor symptoms (items 10–13); sleep refreshment (item 14); and daytime dozing (item 15).[33] The PDSS total score is a sum score of all 15 questions and ranges from 0 to 150, with lower scores meaning more disability.[33] An MCID has not been recognized for the PDSS.

Other non-specific, health-related quality-of-life instruments that may be used in PD clinical trials include Clinical Global Impression rating scales, Patient Global Impression – Improvement Scale (PGI-I), and the Medical Outcomes Study 36-Item Short Form (SF-36).[34] The Clinical Global Impression – Improvement scale (CGI-I) is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to baseline at the beginning of the intervention.[35] The Clinical Global Impression – Severity scale (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis.[35] The PGI-I is a 7-point scale that allows the patient to rate how much their illness has improved or worsened relative to a baseline state at the beginning of the intervention.[36] The SF-36 is a general indicator of function and well-being and includes primarily non-psychiatric health status questions.[37] The SF-36 is a commonly used, reliable and broad-based instrument for a wide variety of medical conditions.[34,37] The MCID thresholds of these instruments in PD patients have not been formally investigated.

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 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, 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.

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:
Systematic reviews were excluded for poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

A systematic review was conducted to identify published RCTs that assessed the efficacy and safety of MAOBIs in patients with PD.[1] Eligible publications included double-blinded RCTs that enrolled patients 18 years and older and compared selegiline, rasagiline or safinamide to each other or to placebo, as monotherapy or

in combination with levodopa therapy.[1] A total of 27 RCTs met inclusion criteria. The investigators were interested in response to MAOBI therapy, defined as the number of patient with at least 20% reduction from baseline to end of study in the UPDRS score or an improvement (minimally improved, much improved or very much improved) on the CGI-I scale.[1] Total UPDRS score was used if provided; otherwise, parts II and III or only part III were evaluated if only these scores were provided.[1] The relative effect of each MAOBI versus the comparator was then compared using a combination of direct and indirect network meta-analyses based on the comparator with levodopa therapy.[1] Overall, there were 4072 patients given a MAOBI, 1489 given placebo, and 1457 given placebo and levodopa therapy. The trials lasted between 6 weeks and 6.5 years, but most lasted up to 24 weeks.[1]

Rasagiline, safinamide and selegiline monotherapy all achieved 20% reduction in UPDRS scores relative to placebo (RR 1.560 (95% CI, 1.409 to 1.734), RR 1.449 (95% CI, 0.873 to 2.413) and RR 1.532 (95% CI, 1.337 to 1.757), respectively).[1] In addition, rasagiline, safinamide, and selegiline given as adjunctive treatment with levodopa therapy all achieved 20% reduction in UPDRS scores relative placebo and levodopa therapy (RR 1.573 (95% CI, 1.369 to 1.803), RR 1.178 (95% CI, 1.031 to 1.350) and RR 2.307 (95% CI, 1.802 to 2.936), respectively).[1] No increased risk for serious adverse events with a MAOBI compared to placebo or joint placebo and levodopa therapy were found.[1]

The investigators concluded all of the MAOBIs were effective compared to placebo, both when given as monotherapy and in combination with levodopa therapy.[1] When given as monotherapy, no significant difference in relative effectiveness between selegiline, rasagiline or safinamide was found.[1] When combination therapy with MAOBIs and levodopa therapy were analyzed, all 3 MAOBIs were effective compared to placebo, but selegiline with levodopa therapy was found to be the most effective combination based on direct and indirect meta-analysis.[1] Most of the included trials used change in UPDRS scores as an efficacy endpoint.[1] However, the investigators remained uncertain of their definition of clinical response and concluded a 20% score reduction in an UPDRS score, which may amount to only a few points in many patients, may not impact an individual's quality of life.[1]

Another systematic review studied the impact of dopaminergic anti-PD drugs on cognitive functioning in mild-to-moderate, non-demented PD patients with compromised or intact cognition.[38] Eligible studies included RCTs or non-randomized studies (e.g., pre-post study) with a control group or within-group comparisons, with or without placebo.[38] Parkinson's disease severity had to be mild to moderate, defined by HY stages 3 or less and a PD duration of 10 years or less at baseline.[38] Results had to be reported on at least one validated cognitive measure before and after the intervention.[38] Exclusion criteria included cohort and case-control studies; case reports and animal model studies; trials including patients presenting with major psychiatric or neurologic disorder besides PD; and PD with dementia per the DSM criteria or an Mini-Mental State Examination (MMSE) score less than 26, as recommended by the Movement Disorder Society.[38] Fourteen studies met inclusion criteria. These studies evaluated levodopa therapy, pramipexole, selegiline and rasagiline. No studies were found that evaluated the effects of ropinirole or COMTIs on cognition.[38]

Overall methodological quality of the studies was low due to small sample sizes, the lack of blinding for patients and data assessors, the absence of power calculations or the lack of concealment of patient allocation.[38] Levodopa therapy showed both statistically significant deleterious and beneficial results on some cognitive outcome measures, most notably in executive functions and episodic memory.[38] Pramipexole was associated with worsening of episodic memory and impulse control.[38] Results on selegiline indicated a deterioration of global cognition over time and of concept formation.[38] Rasagiline had some benefits on working memory and verbal fluency.[38] Overall, the investigators found possible association between dopaminergic anti-PD drugs and cognitive changes in patients with mild-to-moderate PD without dementia.[38] However, they concluded that the inconsistency between studies and their low quality call into question the validity of any association.[38] To better understand whether an association between cognitive function and dopaminergic anti-PD therapy exists, studies of significantly higher methodological quality are required.

The incidences of adverse effects between IR and ER formulations of pramipexole, a dopamine agonist, was systematically reviewed.[2] Eligible studies were double-blinded RCTs that evaluated both IR and ER pramipexole in PD patients and evaluated nausea, dizziness, somnolence and dyskinesia.[2] Out of 81 citations identified, only 3 studies met inclusion criteria. Quality of the 3 studies were assessed based on random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. All 3 trials met quality standards except for concern with performance bias in one trial and attrition bias in another trial. Based on results from 3 trials, there was no significant difference between IR and ER formulations for somnolence [relative risk (RR) = 1.16 (95% CI, 0.95 to 1.43; p=0.14)], nausea [RR = 0.96 (95% CI, 0.72 to 1.28; p=0.80)], or dizziness [RR = 1.11 (95% CI, 0.80 to 1.54; p=0.54)].[2] Only 2 trials reported the incidence of dyskinesia, and no significant difference between IR and ER formulations was found [RR = 0.87 (95% CI, 0.47 to 1.60; p=0.66)].[2]

New Guidelines:
No clinical practice guidelines within this drug class were identified since the last class update.

New Formulations or Indications:
No new formulations or indications within this drug class were identified since the last class update.

New FDA Safety Alerts:
No new safety alerts within this drug class were published by the FDA since the last class update.

Randomized Controlled Trials:
A total of 132 citations were manually reviewed from the initial literature search. Studies were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 3 trials are summarized in **Table 1**. Full abstracts are included in **Appendix 2**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Lee, et al.[39] MC, OL	1. PD-ICD cohort 2. PDTC cohort 3. PDNC cohort	PD diagnosis; age 40-80 y; stable doses of dopaminergic drugs including dopamine agonists >6 months; plus: - PD-ICD: ICD diagnosis developed after anti-PD drug treatment (PD-ICD cohort); or - PDTC: no ICD diagnosis and mMIDI score =0 PDNC: new PD diagnosis; age 40-80 y; never treated for PD Dopamine agonists substituted w/ equivalent dose of levodopa/carbidopa SR tablets and adjusted during 4-week titration period.	Mean Δ mMIDI score (0-12 weeks) in the PD-ICD cohort (other cohorts served as controls and were not compared)	Δ mMIDI = -5.27; p<0.001 vs. baseline in PD-ICD cohort Conclusion: Switching from a dopamine agonist to levodopa/carbidopa SR may alleviate ICD behaviors in patients with PD.
Verschuur, et al.[3] MC, DB, PC, RCT	1. Levodopa/carbidopa 100/25 mg PO TID x80 weeks (early start group) 2. Placebo PO TID x40 weeks, then levodopa/carbidopa 100/25 mg PO TID x40 weeks (delayed start group)	PD diagnosis in past 2 y; insufficient disability to warrant treatment w/ anti-PD drug; age $\geq$30 y; life expectancy >2 y	Mean Δ total UPDRS score (0 to 80 weeks)	1. Early-start Group (n=207): 28.0 $\pm$ 11.2 (baseline) 27.0 $\pm$ 14.8 (week 80) Difference: -1.0 $\pm$ 13.1 2. Delayed-start Group (n=210): 29.0 $\pm$ 11.8 (baseline) 27.0 $\pm$ 14.3 (week 80) Difference: -2.0 $\pm$13.0 Between Group Difference: 1.0 (95% CI, -1.5 to 3.5; p=0.44)

Abbreviations: CI = confidence interval; DB = double blind; HR = Hoehn and Yahr; MC = multi-center; mMIDI = modified Minnesota Impulsive Disorders Interview; OL = open label; PC = placebo-controlled; PD = Parkinson's disease; PD-ICD = Parkinson's disease with Impulse Control Disorder; PDNC = Parkinson's disease drug-naïve control; PDTC = Parkinson's disease treatment control; PO = orally; RCT = randomized controlled trial; SR = sustained release; TID = three times daily; UPDRS = unified Parkinson's disease rating scale; y = years; $\pm$ = standard deviation.

NEW DRUG EVALUATION:

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
The drug sponsor for istradefylline originally submitted a new drug application to the FDA in 2007 but it was not approved out of concern for lack of efficacy.[12] In 4 of the 5 original earlier studies, the primary endpoint was change in "off" time from baseline to 12 weeks (the 5th trial evaluated the primary endpoint at 16 weeks). The drug sponsor had originally submitted 3 RCTs which showed istradefylline, when used as an adjunctive treatment in patients with advanced PD, decreased the percent of daily "off" time in patients.[4-6] However, 2 other adequately sized, well-controlled trials did not demonstrate decrease in "off" time, including an active-controlled study that found benefit with entacapone but not istradefylline.[9,10] In addition, secondary endpoints commonly used to assess symptoms in PD drug trials (e.g., UPDRS, "on" time) or global measures of functioning (e.g., CGI, SF-36) did not find statistically significant benefit with istradefylline versus placebo. The FDA had concern that a lack of consistent benefit in the primary endpoint across multiple studies might suggest either that the effect seen on "off" time was inconsistent or clinically trivial, or that the drug's adverse effects were sufficiently distressing to cause patients' overall judgements to be of no overall benefit.[12] The FDA response indicated that approval would be supported if the drug sponsor was able to demonstrate additional evidence in an adequately designed trial of a decrease in "off" time with istradefylline in patients with advanced PD who were "explicitly maximally and optimally treated with all appropriate available treatments".[12]

Since the original new drug application, the drug sponsor conducted 3 additional RCTs that increase confidence that the gain in "off" time with istradefylline is not obtained at the expense of other benefits like quality of life or functioning.[7,8,11] In total, 8 similarly designed RCTs of istradefylline contributed to the body of evidence reviewed by the FDA for approval as adjunctive treatment to levodopa therapy in patients with PD experiencing "off" episodes.[4-11] All but one 16-week study has a 12-week duration. The data from these clinical trials are summarized and evaluated below in **Table 5**.

Approval of istradefylline was based on 4 of the clinical trials conducted that found positive benefit.[4,6-8] Similar to the other studies, these trials were randomized, multi-center, double-blind, 12-week, placebo-controlled studies. Two trials were conducted in Japan.[7,8] These studies enrolled patients with a mean duration of PD of about 9 years with HY scale of 2 to 4 who experienced at least 2 hours of "off" time per day (mean time was 6 hours per day).[12] All patients were already treated with levodopa for at least one year(dose range 416 to 785 mg/day).[12] Patients continued levodopa therapy with other concomitant PD medications, provided the medication doses were stable for at least 4 weeks before screening and throughout the study period. Concomitant PD medications included dopamine agonists (85%), COMTIs (38%), MAOBIs (40%), amantadine (33%), and anticholinergics (13%).[12]

The primary efficacy endpoint in all of the trials was the change from baseline in daily awake percentage of "off" time, or the change from baseline in total daily "off" time based on 24-hour "on/off" diaries completed by patients. These diaries consisted of 30-minute time periods for 24 hours. Each 30-minute period was classified into the following 5 categories of the patient's condition: Asleep, "off" state, "on" state without dyskinesia, "on" state with nontroublesome dyskinesia, and "on" state with troublesome dyskinesia.

Enrolled patients reported to the clinic to complete 4 consecutive 30-minute periods (and more if necessary) during which the patient had to experience both "on/off" periods. To ensure all enrolled patients were adequately trained, there had to be at least an 80% concordance between the patient's and clinician's ratings of the patient's motor state prior to randomization. Outcome assessments included the review of 2 valid patient diaries completed on any 2 consecutive days during the week prior to the baseline visit and each subsequent visit at weeks 2, 4, 8, and 12. A "valid" patient diary was defined as a diary in which there were no more than 4 incorrect entries (i.e., missing or duplicate entries).

The benefit over placebo in "off" time reduction was 0.7 to 0.9 hour per day, which correlated to a relative reduction of about 15% from "off" time experienced at baseline.[12] Based on evidence submitted to the FDA, there was also an improvement in "on" time without troublesome dyskinesia in patients treated with istradefylline, which supports the benefit found in the primary endpoint of reduction in "off" time.[12] Relative to placebo, the increase in "on" time without troublesome dyskinesia with istradefylline ranged between 0.7 to 1 hour for the 40 mg daily dose, and between 0.6 and 0.8 hour for the 20 mg daily dose.[12] In addition, the FDA emphasized that any clinically meaningful effects on "off" time should be accompanied with an increase in "on" time without troublesome dyskinesia, which would then translate into an improvement on non-specific global or quality of life measures rated by patients. Of the 4 trials the FDA considered for approval, 2 trials found a 2-point benefit with the 40 mg dose in the UPDRS part III "on" state[7,8] and one trial found a 1.7-point benefit in the UPDRS part II "off" state with the 40 mg dose.[8] Other UPDRS sections did not improve with istradefylline, including Part I; Part II "on" and Part IV. Total UPDRS scores also did not differ between istradefylline and placebo.[4] None of the clinical trials found clinically meaningful differences between istradefylline and placebo in improvement of UPDRS scores over 12 weeks of treatment. One trial found improvement in CGI-I, which observed 20.8% and 28.7% felt "much improved" or "very much improved", relative to only 10.7% of patients treated with placebo.[8] Other trials did not find a statistically significant difference in CGI-I, CGI-S, PGI-I, PDQ-39, and SF-36 scores between istradefylline and placebo.[6,7]

Risks of bias for each trial are outlined in **Table 5**. In summary, risk of selection and performance bias is unclear as methodology of randomization and practices to keep group allocation concealed and patients, providers, investigators, and data analysts blinded to the treatment were not described. Symptoms were documented retrospectively in a patient diary and submitted to investigators. While practical for the patient, this may introduce some detection bias depending on the accuracy of the patient's diary entry. A modified intention-to-treat principle was applied, meaning only patients successfully enrolled, randomized and had taken at least one dose of treatment were included in the data analysis. However, because attrition was low prior to administration of first treatment dose, it is doubtful bias could be introduced. Reporting bias was a concern overall. Two studies have not been published and results were not submitted to ClinicalTrials.gov.[10,11] In addition, key secondary endpoints were often presented differently than described in the methods, or were not described at all.[5-7,9] Kyowa Pharmaceuticals provided study funding for all clinical trials.

Overall, there is general applicability of these studies to patients with PD covered under the OHP. Patients had PD with HY scale 2 to 4 and were already optimized on levodopa therapy and 1-2 other PD drugs like a dopamine agonist. Mean ages ranged from 63-66 years of age. Two positive studies considered by the FDA were conducted in Japan, but subgroup analyses conducted by the FDA did not consider lack of efficacy to be an issue in patients specifically from North America. A clear dose response was not observed between the 20 mg and 40 mg doses; however, doses less than 20 mg or more than 40 mg are not recommended based on the studies conducted that evaluated these doses.[5,9]

As is common with short-term Phase 3 clinical trials, there are gaps in evidence with the efficacy of long-term use of istradefylline. Clinical trials were limited to 12 weeks and designed to assess initial efficacy of istradefylline. However, an open-label, 52-week continuation study appears to show that the improvement in "off" time is largely sustained.[40] Comparative trials with other adjunctive PD therapies are also lacking, the exception being a comparison of istradefylline or entacapone versus placebo, which demonstrated statistically superior efficacy of entacapone versus placebo but not with istradefylline.[12] The 0.7 to 0.9 improvement in "off" time observed with istradefylline is within the 0.5 to 2.0 hour range seen with other PD drugs in clinical trials.[12] Based on the demographics of the patients studied, levodopa therapy should be optimized along with at least one additional adjunctive PD drug before a trial of istradefylline is initiated.

Clinical Safety:

The most frequent adverse effects observed in clinical trials (5% or more frequent than placebo) were dyskinesia, dizziness, constipation, nausea, hallucinations and insomnia.[12] **Table 2** summarizes adverse events with an incidence of at least 2% and higher than placebo in patients treated with istradefylline. The drug

sponsor describes the effect of istradefylline as being non-dopaminergic; however, the adverse event profile suggests istradefylline increases dopaminergic activity in the brain.[12] Dyskinesia, hallucinations and dizziness are adverse effects frequently reported in patients treated with medications that increase the effects of dopamine in the central nervous system. Evidence also suggests that istradefylline, like other PD drugs, may increase risk for impulse control disorders.[12] In these clinical studies, rates of impulse control disorders were 0.8% with istradefylline 20 mg and 0.6% with istradefylline 40 mg.[12] Impulse control disorders were not observed in any patients treated with placebo.[12]

Table 2. Adverse Events with an Incidence of at Least 2% in Patients Treated with Istradefylline, and Higher than Placebo.[12]

Adverse Event	PBO (n=426) %	IST 20 mg (n=356) %	IST 40 mg (n=378) %
Nervous System			
Dyskinesia	8	15	17
Dizziness	4	3	6
Gastrointestinal			
Constipation	3	5	6
Nausea	5	4	6
Diarrhea	1	1	2
Psychiatric			
Hallucinations	3	2	6
Insomnia	4	1	6
Nutritional			
Decreased Appetite	1	1	3
Laboratory Data			
↑Blood Alkaline Phosphatase	1	1	2
↑Blood Glucose	0	1	2
↑Blood Urea	0	1	2
Respiratory			
Upper Respiratory Tract Infections	0	1	2
Skin			
Rash	1	1	2

Abbreviations: IST = istradefylline; PBO = placebo

None of the reported deaths during participation in clinical trials were clearly related to istradefylline. Overall, the frequency of serious adverse events was low and similar across all treatment groups (istradefylline 20 mg, 3.9%; istradefylline 40 mg, 4.8%; placebo 3.1%). There were no clinically meaningful changes in vital signs, ECG parameters (e.g., QT interval), hematology, electrolytes or chemistry values in patient enrolled in these trials.

About 90% of patients completed the studies. The percentage of patients who discontinued a study prematurely because of an adverse event was similar between placebo, istradefylline 20 mg and istradefylline 40 mg. The most common adverse events leading to early study discontinuation were nausea/vomiting, (0.4%) and psychosis/delusions/hallucinations (0.4%). **Table 3** summarizes the pooled attrition across all studies and these specific study arms.

Table 3. Pooled Attrition Rates Across all Studies.[12]

Reason for Early Study Discontinuation	PBO (n=1010) %	IST 20 mg (n=869) %	IST 40 mg (n=869) %
Adverse Event	5.4	5.5	7.5
Completed Study	89.8	90.4	89.4
Death	0.5	0	0.3
Lack of Efficacy	0.2	0.2	0.3
Non-compliance with Study Drug	0.2	0	0.3
Other	0.3	0.2	0.2
Physician Decision	0.3	0.3	0
Protocol Deviation	0.6	0.9	0.1
Screen Failure	0.1	0.1	0.1
Withdrawal by Subject	2.8	2.2	1.9

Abbreviations: IST = istradefylline; PBO = placebo

As is common with short-term Phase 3 clinical trials, there are gaps in evidence with the safety of long-term use of istradefylline. Clinical trials were limited to 12 weeks and designed to assess initial efficacy of istradefylline, not the safety of the drug. An open-label, 52-week continuation study reported higher frequencies of the most commonly observed treatment-emergent adverse effects (TEAE) than the 12-week clinical trials.[40] The most commonly reported TEAEs were nasopharyngitis (25.0%) and dyskinesia (25.0%), followed by visual hallucinations (11.0%), contusion (9.0%), and weight decrease (8.0%).[40] Comparative trials with other adjunctive PD therapies are also lacking, so harms cannot be directly compared between istradefylline and other commonly used adjunctive PD drugs. However, early adverse event rates appear to be similar to those observed in short-term clinical trials with other PD drugs. The FDA did not request any further post-marketing requirements.

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

Table 4. Pharmacology and Pharmacokinetic Properties.[41]

Parameter	
Mechanism of Action	Selective adenosine A_{2A} receptor antagonist. These receptors are on the medium spiny neurons of the striatopallidal pathway, which results in an increase in the striatal GABAergic inhibition and decreased release of γ-aminobutyric acid. These changes decrease excessive activation of the striatopallidal output and potential alleviation of motor symptoms of Parkinson's disease.
Oral Bioavailability	Median T_{max} about 4 hours under fasting conditions
Distribution and Protein Binding	The plasma protein binding is about 98% Vd/F = 557 L
Elimination	Total clearance = 4.6 L/h; about 48% in feces and about 39% in urine
Half-Life	C_{max} = 2-5 h; $t_{1/2}$ = 83 h (at steady-state)
Metabolism	Primarily hepatic through CYP3A4 and CYP1A1 pathway; modest CYP3A4 inhibitor

Abbreviations: C_{max} = maximum concentration; h = hours; L = liters; $t_{1/2}$ = half-life; T_{max} = time to reach the maximum concentration; Vd/F = apparent volume of distribution

In patients with moderate hepatic impairment (Child-Pugh B), the steady-state exposure (AUC_{0-24}) of istradefylline is predicted to be 3.3-fold higher relative to healthy patients, based on the estimated mean terminal half-life.[41] No clinically relevant changes in istradefylline exposure were observed in patients with severe renal impairment (creatinine clearance [CrCL] 15-29 mL/min) or mild hepatic impairment.[41] Istradefylline has not been studied in patients with end-stage renal disease (ESRD) (CrCL < 15 mL/min), ESRD patients requiring hemodialysis, or severe hepatic impairment (Child-Pugh C).[41]

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Motor symptoms (e.g., bradykinesia, rigidity, resting tremor)
2) Non-motor symptoms (e.g., autonomic, psychiatric and cognitive impairment)
3) Function (disability and impairment)
4) Health-related quality of life (e.g., PDQ-39)
5) Serious adverse events

Primary Study Endpoint:

1) Change in % "off" time per day at week 12 from baseline

Table 5. Comparative Evidence Table for Istradefylline.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. LeWitt, et al.[4] DB, PC, RCT, MC 12 weeks 6002-US-005	1. istradefylline 40 mg/d 2. placebo 2:1	Demographics: -Mean age: 63 y -Male: 60% -White: 95% -Mean L-dopa dose: ~570 mg/d -Dopa agonist: 86% -Daily OFF state: ~38%; or 7.2 h/d -Daily ON state w/o troublesome dyskinesia: 57.6%; or 9.5 h/d Key Inclusion Criteria: -Idiopathic PD -HY scale 2-4 -L-dopa responsiveness ≥1 y -L-dopa ≥4 doses/d (≥3 doses/d if ≥2 from sustained release formulation) -OFF time ≥2 h/24 h based on home diary -Other PD drugs permitted w/o dose changes Key Exclusion Criteria: NR	ITT: 1. 129 2. 66 PP: 1. 114 2. 58 Attrition: 1. 15 (11.6%) 2. 8 (12.1%)	Primary Endpoint: Δ % OFF state during daily awake time (0-12 weeks) [total hr per day denoted as OFF divided by total hr awake] 1. -10.8% ±16.6% (95% CI, -13.46 to -7.52%) 2. -4.0% ±15.7% (95% CI, -7.73 to 0.31%) LSMD: -6.8% (95% CI, -11.6 to -1.9%; p=0.007) Secondary Endpoints: Δ total hours OFF state during daily awake time (0-12 weeks): 1. -1.8 h ±2.8h (SD) 2. -0.6h ±2.7h (SD) Difference: p=0.006 (CI NR) Δ total hours of daily awake time in ON state w/o troublesome dyskinesia: 1. 1.5 h ±2.9 h (SD) 2. 0.5 h ±2.7 h (SD) Difference: p=0.026 (CI NR) Δ UPDRS evaluations, total of part I-IV (0-12 weeks): 1. -2.0 (SD 8.42) 2. -1.5 (SD 9.97) Difference: p=0.598 (CI NR)	NA NA NA NS	TEAE: 1. 89.1% 2. 86.4% TESAE: 1. 7.8% 2. 1.5% Dyskinesia: 1. 30.2% 2. 15.2% Accidents from Falls: 1. 3.1% 2. 9.1% Study Discontinuation from TEAE: 1. 7.0% 2. 7.6%	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) Method of randomization and concealment of allocation not described; demographics similar between groups. Performance Bias: (unclear) states study was "double blind" but no other details provided. Detection Bias: (high) Patients underwent diary training to record PD states (ON, OFF, ASLEEP). Patients recorded status over each 30-min period during a 24-hour day. ≥80% concordance with investigator's simultaneous ratings during a 5-hr observation trial was needed to verify symptom interpretation and diary training. Patients recorded symptoms in diary for 2 consecutive days during the 7-d period preceding each visit. Attrition Bias: (low) mITT principle applied using LOCF (subjects who took ≥1 dose of study drug); 88% completed study. Reporting Bias: (low) Endpoints provided as described in methods but 95% CI not provided. Other Bias: (high) Kyowa Pharmaceuticals provided study drug but funding of study not disclosed; extent sponsor was involved in study data interpretation was not disclosed. **Applicability**: Patient: All patients took L-dopa; 86% took at least one additional PD drug, most on a dopaminergic agonist. Intervention: FDA-approved dose studied. Study medication compliance "nearly complete". Comparator: Placebo appropriate to establish efficacy of istradefylline. Outcomes: 1.4 hr difference in OFF state between istradefylline and placebo may be clinically significant to PD patients. Setting: 23 clinic sites in US and Canada.

2. Stacy, et al.[5] DB, PC, RCT, MC 12 weeks 6002-US-006	1. Istradefylline 20 mg/d 2. Istradefylline 60 mg/d 3. Placebo 2:2:1	Demographics: -Mean age: 64 y -Male: 67% -Race: NR -Mean L-dopa dose: NR -Dopa agonist: 91% -Daily OFF state: ~35%; or 5.9 h/d -Daily ON state w/o troublesome dyskinesia: ~44.8%; or 7.5 h/d Key Inclusion Criteria: See LeWitt, et al. Key Exclusion Criteria: NR	ITT: 1. 163 2. 155 3. 77 PP: 1. 152 2. 126 3. 69 Attrition: 1. 11 (7%) 2. 29 (19%) 3. 8 (10%)	Primary Endpoint: Δ % OFF state during daily awake time (0-12 weeks): 1. -7.83% (95% CI, -10.05 to -5.60%) 2. -7.96% (95% CI, -10.28 to -5.65%) 3. -3.47% (95% CI, -6.68 to -0.27) LSMD 1 vs. 3: -4.35% (95% CI, -8.16 to -0.54%; p=0.026) LSMD 2 vs. 3: -4.49% (95% CI, -8.35 to -0.62; p=0.024) Secondary Endpoints: Δ daily awake hours OFF (0-12 weeks): 1. -1.24 h (95% CI, -1.62 to -0.86 h) 2. -1.37 h (95% CI, -1.77 to -0.97 h) 3. -0.60 h (95% CI, -1.15 to -0.05 h) Overall treatment effect: p=0.65 (mean differences and 95% CI NR) Δ daily awake hours ON w/o troublesome dyskinesia: Individual group data NR. 1 vs. 3: 0.71 h; p=NS (CI NR) 2 vs. 3: 0.60 h; p=NS (CI NR) Δ UPDRS (0-12 weeks): 1 vs. 3: data NR but p=NS 2 vs. 3: data NR but p=NS Δ CGI-I (0-12 weeks): 1 vs. 3: data NR but p=NS 2 vs. 3: data NR but p=NS	 NA NA NS NS NS NS NS NS NS	TEAE: 1. 60.1% 2. 63.2% 3. 55.8% TESAE: 1. 3.7% 2. 10.3% 3. 6.5% Dyskinesia: 1. 23.9% 2. 22.6% 3. 14.3% Nausea: 1. 20.0% 2. 10.4% 3. 6.5% Dizziness: 1. 11.0% 2. 11.0% 3. 6.5% Hallucinations: 1. 5.2% 2. 4.9% 3. 1.3%	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) See LeWitt, et al. Performance Bias: (unclear) Administered in a "double-dummy" fashion, no other details of blinding provided. Detection Bias: (high) See LeWitt, et al. Attrition Bias: (high) mITT principle applied using LOCF (subjects who took ≥1 dose of study drug); 20% attrition in 60 mg group. Reporting Bias: (high) Primary endpoint and key secondary endpoint provided as described in methods. Missing data for all other secondary efficacy endpoints, including UPDRS and CGI-I. Other Bias: (high) Kyowa Pharmaceuticals developed the research protocol, provided the data set, and conducted the statistical analysis of this clinical trial. Authors were major shareholders, employees or paid consultants for Kyowa Pharmaceuticals. **Applicability**: Patient: All patients took L-dopa; 91% received at least one additional dopaminergic agent. Intervention: 60 mg/d not approved by FDA; ≥95% of subjects in each group ≥90% compliant with study drug. Comparator: placebo appropriate to establish efficacy of istradefylline. Outcomes: 0.64 hr difference in OFF state between istradefylline and placebo may not be clinically significant to PD patients without improvement in functioning or quality of life. No dose response observed in efficacy between 20 mg and 60 mg doses. Setting: 40 clinic sites in North America.

3. Hauser, et al.[6] DB, PC, RCT, MC 12 weeks 6002-US-013	1. Istradefylline 20 mg/d 2. Placebo 1:1	Demographics: -Mean Age: 63.5 y -Male: 66.5% -White: 91.7% -PD Duration: 9.4 y -90% received PD drugs (in addition to L-dopa) -% OFF state per day: 39.8% istradefylline and 38.7% placebo. -Mean L-dopa dose: 642 mg/d Key Inclusion Criteria: See LeWitt, et al. except: -OFF time ≥3 h/24 h based on home diary Key Exclusion Criteria: -Previous istradefylline tx -Atypical or secondary Parkinsonism -Prior neurosurgery for PD -MMSE score <26 -Antipsychotic use in the last 3 months	ITT: 1. 112 2. 113 PP: 1. 104 2. 103 Attrition: 1. 12 (11%) 2. 12 (11%)	Primary Endpoint: Δ % OFF state during daily awake time (0-12 weeks): 1. -9.3% 2. -5.0% LSMD: 4.6% (95% CI, 0.6 to 8.6%; p=0.03) Secondary Endpoints: Δ total hours OFF state during daily awake time (0-12 weeks): 1. 1.6 h (6.7 h to 5.1 h) 2. 0.9 h (6.5 h to 5.7 h) LSMD 0.7 h (95% CI, -1.4 to -0.1 h; p=0.03) Δ UPDRS (0-12 weeks): Part II (activities of daily living), ON state: 1. -0.3 (SD 3.2) 2. -0.9 (SD 3.5); p=0.21 Part II (activities of daily living), OFF state: 1. -1.3 (SD 3.8) 2. -1.6 (SD 3.7); p=0.38 Part III (motor): 1. -3.2 (SD 8.7) 2. -1.9 (SD 8.7); p=0.41 Part II and III total score: 1. -4.7 (SD 12.1) 2. -4.3 (SD 11.7); p=0.97 Δ PDQ-39, SF-36, CGI-S and PGI-I (0-12 weeks): 1. NR for all 2. NR for all, but all p=NS	NA NA NS NS NS NS	TEAE: 1. 79.1% 2. 75.7% Early Discontinuation from AE: 1. 5.2% 2. 6.1% SAE: 1. 3.5% 2. 4.3% Dyskinesia: 1. 22.6% 2. 12.2% Lightheadedness: 1. 7.8% 2. 3.5%	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) Randomization scheduled in blocks of 4 and provided by Aptuit Clinical Packaging and Logistics; demographics similar between groups. Performance Bias: (low) Placebo "matched" the 20-mg istradefylline tablet. The subject, site personnel, and sponsor were blinded to the subject's assigned treatment group. Detection Bias: (low) Clinical monitors and data management personnel were blinded until after the study was complete. Attrition Bias: (high) Efficacy analysis based on mITT (subjects who took ≥1 dose of study drug and who provided at least one valid postbaseline diary). Unclear how missing data or unusable data (nonvalid diary entry) imputed. Reporting Bias: (high) Only primary endpoint disclosed in methods; all other endpoints were not defined a priori. Other Bias: (unclear) Study sponsored by Kyowa Pharmaceutical, Inc. **Applicability**: Patient: All patients took L-dopa; 90% received at least one additional dopaminergic agent. Intervention: FDA-approved dose studied. Adherence rate not disclosed. Comparator: placebo appropriate to establish efficacy of istradefylline. Outcomes: 0.7 hr difference in OFF state between istradefylline and placebo may not be clinically significant to PD patients without an improvement in functioning or quality of life observed. Setting: 26 clinic sites in the U.S.

4. Mizuno, et al.[7] DB, PC, RCT, MC 12 weeks 6002-0608	1. Istradefylline 20 mg/d 2. Istradefylline 40 mg/d 3. Placebo 1:1:1	<u>Demographics</u>: -Mean age: 65 y -Male: 42% -PD Duration: 8 y -Mean L-dopa dose: 1) 407 mg 2) 415 mg 3) 426 mg -Daily OFF time: 1) 6.79 h 2) 6.55 h 3) 6.43 h -Dopamine agonist: 1) 95.7% 2) 91.9% 3) 89.0% <u>Key Inclusion Criteria</u>: -Idiopathic PD -HY scale 2-4 -≥3 doses of L-dopa/DCI per day -L-dopa dose ≥300 mg/d -Stable PD drug regimen -OFF time ≥2 h/24 h based on home diary -Age ≥20 y <u>Key Exclusion Criteria</u>: -Prior neurosurgery for PD -TMS in past 6 months -MMSE score <26 or dementia	<u>ITT</u>: 1. 119 2. 125 3. 119 <u>PP</u>: 1. 106 2. 112 3. 109 <u>Attrition</u>: 1. 13 (11%) 2. 13 (10%) 3. 10 (8%)	<u>Primary Endpoint</u>: Δ total hours OFF state during daily awake time (0-12 weeks): 1. -1.31 h (LSM) 2. -1.58 h (LSM) 3. -0.66 h (LSM) LSMD 1 vs. 3: -0.65 h (95% CI, -1.23 to -0.07h; p=0.013) LSMD 2 vs. 3: -0.92 h (95% CI, -1.49 to -0.35h; p<0.001) <u>Secondary Endpoints</u>: CGI-I: "Much Improved": 1. 20.9% 2. 23.4% 3. 14.4% "Minimally Improved": 1. 56.5% 2. 56.5% 3. 46.6% Overall CGI-I Improvement: 1 vs. 3: p=0.074 (CI NR) 2 vs. 3: p=0.096 (CI NR) Δ UPDRS Part I-III total score: NR Δ UPDRS part III ON state (0-12 weeks): 1. -5.7 (LSM) 2. -5.7 (LSM) 3. -3.7 (LSM) 1 vs. 3: -2.0; p=0.006 (CI NR) 2 vs. 3: -2.0; p=0.006 (CI NR) Δ ON state w/o troublesome dyskinesia (0-12 weeks): NR 1. 0.57h[12] 2. 0.65h[12] 3. NR 1 vs. 3: NR 2 vs. 3: "nominal" p<0.05[12]	NA NA NS NS NA NA NA NA NA	TEAE: 1. 59.3% 2. 59.2% 3. 58.0% <u>Dyskinesia</u>: 1. 8.5% 2. 6.4% 3. 2.5% <u>Nasopharyngitis</u>: 1. 5.9% 2. 8.8% 3. 4.2%	NA	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: (unclear) Method of randomization and concealment of allocation not described; demographics similar between groups. <u>Performance Bias</u>: (unclear) Only states the study was "double blind". <u>Detection Bias</u>: (high) 95% CI not provided for endpoints; unclear if data analysists blinded. <u>Attrition Bias</u>: (high) mITT applied (≥1 dose received + ≥1 set of diaries submitted). Missing values at week 12 or early termination were imputed using LOCF. <u>Reporting Bias</u>: (high) Several key secondary endpoints related to functioning and ON state without dyskinesia not disclosed as outlined in methods. <u>Other Bias</u>: (unclear) Study supported by an unrestricted research grant from Kyowa Hakko Kirin CO., Ltd., Japan. **Applicability**: <u>Patient</u>: Only Japanese patients studied. All patients took L-dopa; >90% received at least one additional dopaminergic agent. <u>Intervention</u>: FDA-approved doses studied but no dose-response observed. Adherence rate not disclosed. <u>Comparator</u>: Placebo appropriate to establish efficacy of istradefylline. <u>Outcomes</u>: Difference in efficacy between 20 mg and 40 mg doses not observed; the 0.65 h and 0.92 h differences in OFF state between istradefylline doses and placebo may not be clinically significant to PD patients without improvement in quality of life; some function improvement reported, but lack of reporting of several key secondary endpoints makes interpretation difficult. <u>Setting</u>: 47 clinic sites in Japan.

5. Mizuno, et al.[8] DB, PC, RCT, MC 12 weeks 6002-009	1. Istradefylline 20 mg/d 2. Istradefylline 40 mg/d 3. Placebo 1:1:1	Demographics: -Mean age: 66 y -Male: 44% -PD Duration: 7.7 y -Mean L-dopa dose: 1) 431 mg 2) 421 mg 3) 425 mg -Daily OFF time: 1) 6.55 h 2) 5.97 h 3) 6.31 h -Dopamine agonist: 1) 85.8% 2) 83.7% 3) 91.1% -Daily "on" time without troublesome dyskinesia: 1) 1.00 h 2) 1.13 h 3) 0.94 h Key Inclusion Criteria: See Mizuno[7] Key Exclusion Criteria: See Mizuno[7]	ITT: 1. 120 2. 123 3. 123 PP: N=373 (groups NR) Attrition: 7 subjects total (groups NR)	Primary Endpoint: Δ total hours OFF state during daily awake time (0-12 weeks): 1. -0.99 h (LSM) 2. -0.96 h (LSM) 3. -0.23 h (LSM) LSMD 1 vs. 3: -0.76 h (95% CI, -1.30 to -0.22 h; p=0.003) LSMD 2 vs. 3: -0.74 h (95% CI, -1.27 to -0.20 h; p=0.003) Secondary Endpoints: Δ Daily ON state w/o troublesome dyskinesia: 1. 1.09 h 2. 1.08 h 3. 0.26 h LSMD 1 vs. 3: 0.83 h (CI NR) (p=0.003) LSMD 2 vs. 3: 0.81 h (CI NR) (p=0.004) Δ UPDRS Part I-IV total score: NR Δ Part I: p=NS for all Δ Part II ON: p=NS for all Δ Part II OFF: 1 vs. 3 p=NS; 2 vs. 3 = -1.7 (p=0.009) Δ Part III ON: 1 vs. 3 p=NS; 2 vs. 3 = -2.0 (p=0.001) Δ Part IV: p=NS for all CGI-I: "Much Improved" and "Very much Improved": 1. 20.8% (p=0.005 vs. 3) 2. 28.7% (p<0.01 vs. 3) 3. 10.7%	NA NA NA NA NS NS NS NA NS NA NS NA NA	TEAE: 1. 65.0% 2. 59.7% 3. 51.6% SAE: 1. 5.0% 2. 4.9% 3. 1.6% Dyskinesia: NR		**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) Method of randomization and concealment of allocation not described; demographics similar between groups. Performance Bias: (unclear) Only states the study was "double blind". Detection Bias: (unclear) 95% CI not provided for endpoints; unclear if data analysts were blinded. Patients completed diaries for 7 consecutive days before visits in weeks 2, 4, 8 and 12. Attrition Bias: (unclear) mITT defined as patients who received ≥1 dose and submitted 4 valid diaries for evaluation. Attrition rates in each group are unclear. Unclear how missing data were imputed. Reporting Bias: (low) Endpoints reported as outlined in methods but some secondary endpoints were emphasized more than others. Other Bias: (unclear) Study supported by an unrestricted research grant from Kyowa Hakko Kirin CO., Ltd., Japan. **Applicability**: Patient: Only Japanese patients studied. All patients took L-dopa; >90% received at least one additional dopaminergic agent. Intervention: FDA-approved doses studied but no dose-response observed. Adherence rate not disclosed. Comparator: Placebo appropriate to establish efficacy of istradefylline. Outcomes: Difference in efficacy between 20 mg and 40 mg doses not observed; the 0.76 h and 0.74 h differences from istradefylline and placebo in OFF state may not be clinically significant to PD patients. Safety outcomes not clearly reported. Setting: 44 clinic sites in Japan.

6. Pourcher, et al.[9] DB, PC, RCT, MC 12 weeks 6002-US-018	1. Istradefylline 10 mg/d 2. Istradefylline 20 mg/d 3. Istradefylline 40 mg/d 4. Placebo 1:1:1:1	Demographics: -Mean age: 63 y -Male: 67% -White: 93% -PD Duration: 8.9 y -Mean % time in OFF state: 40.2% (6.7 h) -Mean L-dopa dose: 663 mg/d Key Inclusion Criteria: -Age ≥30 y -UKPDS criteria for PD diagnosis - HY scale 2-4 in OFF state -Mean ≥180 min/d in OFF time -≥3 doses/d of L-dopa for ≥1 y -Predictable end-of-dose wearing-off -Stable PD regimen for ≥4 weeks Key Exclusion Criteria: NR	ITT: 1. 155 2. 149 3. 152 4. 154 PP: 1. 149 2. 144 3. 145 4. 146 Attrition: 1. 19 (12.4%) 2. 18 (12.1%) 3. 17 (11.2%) 4. 14 (9.3%)	Primary Endpoint: Δ % OFF state during daily awake time (0-12 weeks): 1. -5.7% 2. -6.1% 3. -9.1% 4. -7.6% (p=0.475 vs 2 and 3) Secondary Endpoints: Δ total hours OFF state during daily awake time (0-12 weeks): 1. -1.0 h 2. -1.1 h 3. -1.5 h 4. -1.3 h (p=0.529 vs 2 and 3) Δ total hours per day awake in ON state (w/ and w/o dyskinesia and w/ and w/o nontroublesome dyskinesia): NR but p=NS for all Δ UPDRS Part II ON state (0-12 weeks): 1. -0.5 (SD 3.7); 2. -0.2 (SD 3.4); 3. -0.7 (SD 3.8); 4. -0.6 (SD 3.6); overall p=0.961 Δ UPDRS Part II OFF state (0-12 weeks): 1. -1.0 (SD 4.2); 2. -1.8 (SD 4.6); 3. -1.4 (SD 4.0); 4. -2.1 (SD 3.8); overall p=0.085 Δ UPDRS Part III ON state (motor scale) (0-12 weeks): 1. -0.8 (SD 8.5); 2. -1.0 (SD 6.9); 3. -0.8 (SD 8.2); 4. -2.9 (SD 9.9); Overall p=0.042 (CI NR) SF-36 (0-12 weeks): Data NR but 2 vs. 4, p=0.003 and 3 vs. 4, p=0.009	NS NS NS NS NA NA	TEAE: 1. 82.4% 2. 83.9% 3. 84.2% 4. 76.2% Early Discontinuation from TEAE: 1. NR 2. 10.1% 3. 9.2% 4. 4.2% Dyskinesia: 1. 21.6% 2. 16.8% 3. 26.3% 4. 19.2% Insomnia: 1. 6.5% 2. 7.4% 3. 10.5% 4. 7.3% Worsened PD: 1. 11.1% 2. 6.0% 3. 4.6% 4. 5.3%	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) Method of randomization and concealment of allocation not described; demographics similar between groups. Performance Bias: (unclear) the study used a "matching placebo" and stated the patient, site personnel, and the study sponsor were blinded to group assignments. Detection Bias: See LeWitt, et al. Attrition Bias: (low) mITT defined as patients who received ≥1 dose and had 1 valid baseline and ≥1 valid post-baseline diary assessment; missing data analyzed by LOCF. Reporting Bias: (high) Several secondary outcomes not reported except to note study drug was not statistically different from placebo. Overall p-values between all doses given without confidence intervals; unclear how individual groups statistically compare vs. placebo based on overall treatment p-values. Other Bias: (high) Kyowa Hakko Kirin Pharma, Inc., developed the research protocol, provided the data set, and conducted the statistical analysis of the trial. Multiple authors received compensation from Kyowa Hakko Kirin Pharma, Inc. **Applicability**: Patient: All patients took L-dopa; 90% took at least one additional dopaminergic agent. Intervention: FDA-approved 20 mg and 40 mg doses studied. Some dose-response observed but difficult to interpret with similar response from placebo. Adherence rate not disclosed. Comparator: Placebo appropriate to establish efficacy of istradefylline. Outcomes: Study unable to find statistically significant differences between study drug doses and placebo. Setting: 59 sites in the U.S. and 15 sites in Canada.

7. NCT 00199394[10,42] DB, PC, RCT, MC 16 weeks 6002-EU-007	1. Istradefylline 40 mg/d 2. Entacapone 200 mg w/ each L-dopa dose 3. Placebo 1:1:1	<u>Demographics</u>: NR <u>Key Inclusion Criteria</u>: -Age ≥30 y -UKPDS criteria for PD diagnosis - HY scale 2-4 in OFF state -Mean ≥180 min/d in OFF time -≥3 doses/d of L-dopa for ≥1 y -Predictable end-of-dose OFF episodes -Stable PD regimen for ≥4 weeks <u>Key Exclusion Criteria</u>: -Dopamine antagonist or investigational drug w/i 30 d -Psychotic illness -Atypical or secondary parkinsonism -Cancer in past 5 y	N=405	<u>Primary Endpoint</u>: Δ % OFF state during daily awake time (0-16 weeks): 1. -5.14% 2. -7.82% 3. -4.53% 1 vs. 3: p=NS per FDA[12] 2 vs. 3: p<0.05 per FDA[12] <u>Secondary Endpoints</u>: Δ % ON state during daily awake time (also w/ and w/o dyskinesia and w/ and w/o nontroublesome dyskinesia): 1 vs. 3: p=NS 2 vs. 3: NR Δ UPDRS Part III score (motor subscale): 1 vs. 3: p=NS 2 vs. 3: NR	NS NA NS NR NS NR	<u>TEAE</u>: 1. 64.8% 2. 66.0% 3. 63.8% <u>SEA</u>: 1. 3.1% 2. 3.3% 3. 3.9% <u>Early Discontinuation from AE:</u> 1. 4.4% 2. 6.5% 3. 6.6%		Note: Study completed but unpublished so risk of bias and applicability of study unclear. Results not submitted to ClinicalTrials.gov and are provided by drug sponsor's dossier.

8. NCT 01968031[11,42] DB, PC, RCT, MC 12 weeks 6002-014	1. Istradefylline 20 mg/d 2. Istradefylline 40 mg/d 3. Placebo 1:1:1	<u>Demographics</u>: NR <u>Key Inclusion Criteria</u>: -Age ≥30 y -UKPDS criteria for PD diagnosis - HY scale 2-4 in OFF state -Mean ≥180 min/d in OFF time -≥3 doses/d of L-dopa for ≥1 y -Predictable end-of-dose OFF episodes -Stable PD regimen for ≥4 weeks <u>Key Exclusion Criteria</u>: -Apomorphine, dopamine antagonist, direct GI L-dopa infusion, anticholinergic agents, amantadine alone, or investigational drug w/i 30 d -H/o psychotic illness -H/o sleep attacks -Neurosurgery for PD -Previously treated with istradefylline -CYP3A4 inhibitors and inducers	N=613	<u>Primary Endpoint</u>: Δ total hours OFF state during daily awake time (0-12 weeks): 1 vs. 3: -0.32 h; p=0.156 2 vs. 3: -0.27 h; p=0.234 <u>Secondary Endpoints</u>: Δ total hours ON state w/o troublesome dyskinesia during daily awake time (0-12 weeks): 1 vs. 3: 0.24 h; p=0.366 2 vs. 3: 0.00 h; p=0.986	 NS NS NS NS	<u>TEAE</u>: 1. 58.7% 2. 64.7% 3. 55.9% <u>SEA</u>: 1. 3.0% 2. 3.9% 3. 3.4% <u>Early Discontinuation from AE:</u> 1. 5.0% 2. 10.6% 3. 6.4%		Note: Study completed but unpublished so risk of bias and applicability of study unclear. Results not submitted to ClinicalTrials.gov and are provided by drug sponsor's dossier.

<u>Abbreviations</u>: ARR = absolute risk reduction; CGI-I = Clinical Global Impressions – Improvement in illness scale; CGI-S = Clinical Global Impressions – Severity of Illness Scale; CI = confidence interval; d= days; DB = double blind; DCI = decarboxylase inhibitor (e.g., carbidopa); GI = gastrointestinal; H/o = history of; HY = Hoehn & Yale scale; ITT = intention to treat; L-dopa = levodopa; LOCF = last observation carried forward; LSM = least-square mean; LSMD = least-square mean difference; MC = multicentered; mg = milligrams; mITT = modified intention to treat; MMSE = Mini-Mental State Examination; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; PC = placebo controlled; PD = Parkinson's Disease; PDQ-39 = Parkinson's Disease Questionnaire; PGI-I = Patient Global Impression – Improvement Scale; PP = per protocol; RCT = randomized controlled trial; SD = standard deviation; SF-36 = Medical Outcomes Study 36-Item Short Form; TEAE = treatment-emergent adverse effects; TESAE = treatment-emergent serious adverse effects; TMS = transcranial magnetic stimulation; UKPDS = United Kingdom's Parkinson's Disease Society; UPDRS = Unified Parkinson Disease Rating Scale; y = years.

NEW DRUG EVALUATION:

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
The efficacy and safety of opicapone 25 mg and 50 mg daily was established in two identical double-blind, randomized, placebo-controlled trials (Studies 301 and 302) in patients with idiopathic PD and motor fluctuations already treated with levodopa therapy.[13,14] Key inclusion and exclusion criteria are listed in **Table 8**. In both studies, patients were eligible if they were between 30 and 83 years of age with a minimum duration of PD of at least 3 years.[13,14] Patients had to be in HY stages 1 to 3 during an "on" state and had to have at least 1.5 hours of "off" time per day.[13,14] The primary differences in Study 301 were the addition of a 5 mg opicapone arm and an entacapone arm, which served as an active control to assess non-inferiority of opicapone.[13] Each study included multiple study centers across several countries, but no sites in North America participated.[13,14] Patients were mostly male (~60%), White (100% in Study 301), with an average age of about 64 years and "off" time of about 6.2-6.5 hours per day.[13,14] Mean daily levodopa doses were 700 to 800 mg and most patients were also on a dopamine agonist.[13,14]

The primary efficacy endpoint for both studies was the total reduction in daily "off" time assessed at 14-15 weeks (visit 7), which was assessed using 24-hour patient diaries in which patients recorded their status as "off", "on" with troublesome dyskinesia, "on" with non-troublesome dyskinesia, "on" without dyskinesia, or "asleep" for every 30-minute interval for the 3 consecutive days before each clinic visit.[13,14] Opicapone 50 mg daily reduced "off" time by 54-61 minutes per day versus placebo (study 301: mean difference [MD] = -60.8 min [95% CI, -97.2 to -24.4]; and study 302: MD = -54.3 min [95% CI, -96.2 to -12.4]).[13,14]

The benefit associated with a reduction in absolute "off" time found with the opicapone 50 mg dose must be balanced with a potential increase in "on" time without troublesome dyskinesia. The FDA review of the clinical data found that reduction in "off" time was supported by an increase in "on" time without troublesome dyskinesia for the 50 mg dose.[21] The 25 mg dose of opicapone did not reach statistical significance versus placebo in either study.[13,14] The 50 mg dose was found to be non-inferior to entacapone in study 301 (see **Table 8** for details).[13]

Key pre-specified secondary endpoints included change in total UPDRS; change in the Parkinson's Disease Sleep Scale (PDSS), a specific scale used to assess sleep disturbances in patients with PD; and a Non-motor Symptoms Scale (NMSS), all assessed at 14-15 weeks.[21] Quality of life was also assessed using the PDQ-39 questionnaire.[13,14] Neither study found statistically significant differences between doses of opicapone studied and placebo for these key secondary endpoints.[13,14]

As outlined in **Table 8**, both studies were limited by their applicability to the Oregon Medicaid population and concern for potentially high risk of detection and reporting bias.

Clinical Safety:

The most common reason for early withdrawal from the trials was adverse events.[13,14] Eight percent of patients treated with opicapone 50 mg discontinued because of an adverse event in studies 301 and 302, with 4% withdrawing early in Study 301 and 12% withdrawing early in Study 302.[13,14] Among patients treated with opicapone 50 mg, dyskinesia was the most common adverse event leading to early study discontinuation (3%), contrasting with no discontinuations for dyskinesia in the placebo arms.[21] Two percent of patients treated with opicapone 50 mg discontinued because of nausea or vomiting, compared with 0.4% of patients on placebo.[21] Five percent of patients treated with opicapone 50 mg experienced at least one serious adverse event in both studies, compared to 4% of patients on placebo.[21]

Dyskinesia and constipation were the most common adverse events observed in both studies (see **Table 6**).[21] A dose-response for dyskinesia, constipation, and elevated blood creatine phosphokinase was found in the opicapone arms.[21] In both studies, 2% of patients treated with opicapone 50 mg developed an impulse control disorder versus zero patients in the placebo arms.[21] The incidence of sleep attacks and somnolence was not greater in patients treated with opicapone than on placebo.[21]

Table 6. Adverse Events reported in ≥2% of Patients Treated with Opicapone 50 mg and With a Higher Incidence Than Placebo.[21]

Adverse Event	Opicapone 50 mg/day (n=265) %	Placebo (n=257) %
Nervous System Disorders		
Dyskinesia	20	6
Dizziness	3	1
Gastrointestinal Disorders		
Constipation	6	2
Dry Mouth	3	1
Psychiatric Disorders		
Hallucination	3	1
Insomnia	3	2
Vascular Disorders		
Hypertension	3	2
Hypotension/Syncope	5	2
Other		
Increased Blood Creatinine Phosphokinase	3	2
Decreased Weight	5	2

Few patients had abnormal ECG findings. In the opicapone 50 mg arm, 5.1% had an QTc greater than 480 milliseconds, versus 2.1% on placebo.[21]

Creatine kinase (CK) was elevated to at least 3-times the upper limit of normal in 5.4 % of patients treated with opicapone 50 mg, compared with 1.7% on placebo.[21] Two patients treated with opicapone discontinued the study early because of elevated CK.[21]

In both trials, dyskinesia, constipation, urinary tract infection, headache, and dry mouth were more common in females and in patients 65 years of age or older treated with opicapone 50 mg.[21] Elevated CK was observed more frequently in Asian patients than in White patients (9% vs. 4%), but the relatively small number of Asian patients studied limits the interpretability of that observation.[21]

Overall, the safety profile of opicapone is consistent with its mechanism of action, with adverse reactions mostly mediated by increased exposure to levodopa and dopamine. The safety profile is similar to entacapone and tolcapone, but in contrast with tolcapone, with no identified significant hepatic toxicity.[21]

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

Table 7. Pharmacology and Pharmacokinetic Properties.[20,21]

Parameter	
Mechanism of Action	Catechol-O-methyltransferase (COMT) inhibition, thereby increasing systemic exposure to levodopa.
Oral Bioavailability	Not determined. Repeat daily dosing of opicapone 50 mg with administration of carbidopa/levodopa every 3 or 4 hours increased levodopa C_{max} by 43-44% and AUC by 62-94%.[21] The administration of opicapone 50 mg with a high fat meal decreased the opicapone C_{max} and AUC by 62% and 31%, respectively, and delayed the median T_{max} by 4 hours compared to opicapone administration under fasted conditions.[21] Labeling for opicapone recommends that patients not eat food for at least one hour before and after taking opicapone.
Distribution and Protein Binding	Opicapone is highly bound to plasma proteins (>99%), which is independent of serum concentration.
Elimination	About 70% of a dose of opicapone is eliminated in the feces (22% unchanged) and 5% in urine (<1% unchanged). No clinically significant differences in the pharmacokinetics of opicapone were observed in patients with mild to moderate renal impairment. No dosage adjustment is required for patients with mild, moderate, or severe renal impairment. Avoid use of in patients with ESRD (Cl_{CR} <15 mL/min).
Half-Life	The mean elimination half-life of opicapone is 1 hour.
Metabolism	Sulfation is the primary metabolic pathway of opicapone. Other metabolic pathways include glucuronidation, methylation (by COMT), reduction, and glutathione conjugation.

Abbreviations: AUC = area under the curve; C_{max} = maximum concentration; Cl_{CR} = creatinine clearance; COMT = catechol O-methyl transferase; ESRD = end stage renal disease; h = hours; L = liters; $t_{1/2}$ = half-life; T_{max} = time to reach the maximum concentration; Vd/F = apparent volume of distribution

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Motor symptoms (e.g., bradykinesia, rigidity, resting tremor)
2) Non-motor symptoms (e.g., autonomic, psychiatric and cognitive impairment)
3) Function (disability and impairment)
4) Health-related quality of life (e.g., PDQ-39)
5) Serious adverse events

Primary Study Endpoint:

1) Change in time per day in "off" state

Table 8. Comparative Evidence Table for Opicapone.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Ferreira, et al. Study 301 DB, AC, NI, PC, RCT, MC 14-15 weeks	1. Opicapone PO 5 mg QHS 2. Opicapone PO 25 mg QHS 3. Opicapone PO 50 mg QHS 4. Entacapone 200 mg w/ each L-dopa dose 5. Placebo PO daily 1:1:1:1:1	Demographics: -Mean age: 64 y -Male: 59% -White: 100% -Mean L-dopa dose: 662 mg/d -Dopa agonist: 67.5% -Daily OFF state: 40%; or 6.5 h/d -Daily ON state w/o troublesome dyskinesia: 6.4%; or 0.3 h/d HY stage during ON state: 2.4 Key Inclusion Criteria: -Age 30-83 y -PD ≥3 y -HY scale 1-3 during ON state -L-dopa use ≥1 y -Stable doses of L-dopa and other PD drug regimens ≥4 wks -Awake OFF state ≥1.5 hr/day, excluding morning akinesia Key Exclusion Criteria: -Previous use of entacapone	ITT: 1. 122 2. 119 3. 116 4. 122 5. 121 PP: 1. 110 2. 105 3. 106 4. 104 5. 112 Attrition: 1. 9.8% 2. 9.2% 3. 7.8% 4. 14.8% 5. 7.4%	Primary Endpoint: Δ time in OFF state (baseline to 14-15 wks) 1. -91.3 min (95% CI, -117.5 to -64.8 min) 2. -85.9 (95% CI, -112.8 to -59.1 min) 3. -116.8 min (95% CI, -144.2 to -89.4) 4. -96.3 min (95% CI, -122.6 to -70.0) 5. -56.0 min (95% CI, -82.3 to -29.7) MD Vs. Placebo (95% CI): 1. -35.2 min (-71.4 to 0.9) 2. -29.9 min (-66.3 to 6.5) 3. -60.8 min (-97.2 to -24.4) 4. -40.3 min (-76.2 to -4.3) 3 vs. 4: MD -26.2 min (95% CI -63.8 to 11.4) meeting NI Secondary Endpoints: Δ UPDRS total score (p-value vs. placebo [95% CI NR]) 1. -7.3 (p=0.13) 2. -7.0 (p=0.19) 3. -6.1 (p=0.56) 4. -6.1 (p=0.56) 5. -5.4	 NS NS NA NA NA NS NS NS NS	TEAE: 1. 52% 2. 55% 3. 54% 4. 57% 5. 50% Serious TEAE: 1. 3% 2. 1% 3. 3% 4. 5% 5. 7% Dyskinesia: 1. 14% 2. 8% 3. 16% 4. 8% 5. 4% Hallucinations: 1. 2% 2. 8% 3. 4% 4. 1% 5. 2% Study Discontinuation from TEAE: 1. 6%	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized by computer-generation by blocks of 8-10 depending on regimen, stratified by center; demographic characteristics evenly matched. Performance Bias: (low) patients and investigators blinded to treatment allocation; masking maintained by use of identical over-encapsulation of opicapone and entacapone tablets; placebo matched appearance of opicapone and entacapone and included riboflavin to mimic urinary discoloration caused by entacapone. Daytime doses of active drugs given concomitantly w/ L-dopa (ie, 3-8 daily doses); additional QHS dose administered at least 1 h after last daily dose of L-dopa. Opicapone arms took placebo for the daytime doses and active tx QHS. Entacapone group took active tx during the day and placebo at QHS. Detection Bias: (high) unknown if data assessors blinded; endpoints dependent on accuracy/recall of patient diaries; tested superiority of each opicapone dose vs. placebo in the mITT analysis data set and non-inferiority vs. entacapone in the PP data set (non-inferiority margin of 30 min). 106 participating centers w/ 600 enrolled patients between 2011-2013 might be a source of practice variations; low rate of enrollment may suggest inclusion into the trial was overly selective. Attrition Bias: (low) overall attrition <10% in most study arms but entacapone arm; however, mITT used to analyze efficacy data in patients who took

		-UPDRS item 33 (disability) score >3 (range 0-4) -Severe and/or unpredictable OFF state -Previous surgery or deep brain stimulation for PD -h/o NMS or rhabdomyolysis -Clinically significant CV or psychiatric illness -Concomitant tolcapone, apomorphine, neuroleptics, venlafaxine, MAOBI (except selegiline up to 10 mg/d PO or 1.25 mg/d buccal and rasagiline up to 1 mg/d), antiemetic w/ antidopamine properties		Δ PDSS score (p-value vs. placebo [95% CI NR]) 1. 5.2 (p=0.09) 2. 5.5 (p=0.07) 3. 2.9 (p=0.45) 4. 2.9 (p=0.45) 5. 1.0 Δ NMSS score (p-value vs. placebo (95% CI NR]) 1. -5.6 (p=0.98) 2. -4.2 (p=0.45) 3. -2.0 (p=0.90) 4. -4.7 (p=0.63) 5. -5.7 Δ % time in ON state w/o troublesome dyskinesia: 1. 9.1% 2. 8.8% 3. 10.8% 4. 9.6% 5. 5.4% MD Vs. Placebo (95% CI): 1. 3.7% (-0.1 to 7.6%) 2. 3.5% (-0.4 to 7.4%) 3. 5.4% (1.5 to 9.3%) 4. 4.2% (0.4 to 8.1%)	NS NS NS NS NS NS NS NS NS NS NA NA	2. 7% 3. 4% 4. 7% 5. 7%		≥1 dose of study drug and had ≥1 assessment of time in OFF state after baseline; compliance w/ diary entries ranged from 90-100%; LOCF used to impute missing diary data. Reporting Bias: (high) key pre-specified secondary endpoints registered with the NIH were not emphasized in publication; alternate secondary endpoints around ON/OFF times were emphasized; 95% CI not reported for key secondary endpoints. Other Bias: (high) authors employed by drug sponsor and participated in the study design, data collection, data management, and data analysis. **Applicability**: Patient: Composed of Russians and Europeans without non-White representation; no U.S. citizens in study. Patients were mostly older males on L-dopa and a dopamine agonist. PD course for most was mild to moderate, with bilateral disease without balance difficulties. Intervention: Dose range study used to determine efficacy of opicapone. Findings suggest only the 50 mg dose has efficacy. Comparator: Both placebo and active comparator entacapone used to establish efficacy. Opicapone 50 mg was non-inferior to entacapone suggesting opicapone is another COMTI tx option. Outcomes: Opicapone evaluated specifically for L-dopa end-of-dose wearing off; 50 mg dose decreased time in OFF state by 1 hr/day and increased time in ON state without troublesome dyskinesia. However, these changes had no impact on functional status or quality of life. Setting: 106 centers in Europe and Russia.
2. Lees, et al.[14] Study 302 DB, PC, RCT, MC 14-15 weeks	1. Opicapone PO 25 mg QHS 2. Opicapone PO 50 mg QHS 3. placebo 1:1:1	Demographics: -Mean age: 63.1 y -Male: 60.4% -White: 67.3% -Mean L-dopa dose: 700-806 mg/d -Dopa agonist: 69.5% -Daily OFF state: ~38%; or 6.2 h/d -Daily ON state w/o troublesome	ITT: 1. 129 2. 154 3. 144 PP: 1. 118 2. 128 3. 130 Attrition:	Primary Endpoint: Δ time in OFF state (baseline to 14-15 wks) 1. -101.7 min (SD 14.9) 2. -118.8 min (SD 13.8) 3. -64.5 min (SD 14.4) MD vs. Placebo (95% CI): 1. -37.2 min (-80.8 to 6.4) 2. -54.3 min (-96.2 to -12.4)	NS NA	TEAE: 1. 69.6% 2. 72.0% 3. 64.0% TESAE: 1. 3.2% 2. 6.0% 3. 3.7% Dyskinesia:	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) patients randomized by interactive web response system using blocks stratified by region. Placebo had fewer males and more Asian patients compared to active treatment arms. Performance Bias: (low) opicapone doses and placebo were identically encapsulated to maintain blinding. Detection Bias: (high) data analyzed by mITT (≥1 dose received and ≥1 post-baseline assessment);

		dyskinesia: ~58%; or 9.4 h/d Key Inclusion Criteria: See Ferreira, et al. Key Exclusion Criteria: See Ferreira, et al.	1. 8.5% 2. 16.9% 3. 9.7%	Secondary Endpoints: Δ UPDRS total score (p-value vs. placebo [95% CI NR]) 1. -4.4 (p=0.37) 2. -3.5 (p=0.45) 3. -3.5 Δ PDSS score (p-value vs. placebo) 1. 2.5 (p=0.29) 2. 2.3 (p=0.23) 3. 5.1 Δ NMSS score (p-value vs. placebo) 1. -2.0 (p=0.13) 2. -4.9 (p=0.88) 3. -5.2 Δ time in ON state w/o troublesome dyskinesia: 1. 84.1 min 2. 85.6 min 3. 48.1 min MD vs. Placebo (95% CI): 1. 36.0 min (-5.6 to 77.5) 2. 37.4 min (-2.4 to 77.2)	 NS NS NS NS NS NS NS NS	1. 24.0% 2. 24.0% 3. 8.1% Falls: 1. 5.6% 2. 4.7% 3. 6.6% Study Discontinuation from TEAE: 1. 4.0% 2. 12.0% 3. 7.4% Constipation: 1. 9.6% 2. 6.7% 3. 1.5%		unknown if data assessors blinded. Endpoints dependent on accuracy/recall of patient diaries; 71 participating centers w/ 485 enrolled patients between 2011-2013 might be concern for practice variation; low rate of enrollment may suggest inclusion into the trial was overly selective. Attrition Bias: (high) 17% attrition in opicapone 50 mg arm; diary compliance not disclosed; LOCF method used for missing data. Reporting Bias: (high) Key pre-specified secondary endpoints registered with the NIH were not emphasized, rather alternate endpoints around ON/OFF times were emphasized; 95% CI not reported for key secondary endpoints. Other Bias: (high) study was funded by the drug sponsor; authors received funding or were employed by drug sponsor. **Applicability**: Patient: Patients on stable doses of L-dopa with mild to moderate PD without balance difficulties; study did not include any participants from North America; age and gender balanced for PD. Intervention: Opicapone 50 mg demonstrated efficacy at decreasing OFF time vs. placebo with increased risk of adverse events and attrition. The 25 mg dose did not demonstrate efficacy. Comparator: Placebo was appropriate to establish efficacy in a Phase 3 trial. Outcomes: 50 mg dose decreased time in OFF state by 54 min daily but unclear if ON state without troublesome dyskinesia improved. No impact on functional status or quality of life was observed. Setting: 71 centers in 12 counties (no sites in North America).

Abbreviations: AC = active controlled; ARR = absolute risk reduction; CI = confidence interval; COMTI = Catechol-O-methyltransferase inhibitor; d = days; DB = double blind; GI = gastrointestinal; H/o = history of; HY = Hoehn & Yale scale; ITT = intention to treat; L-dopa = levodopa; LOCF = last observation carried forward; MAOBI = monoamine oxidase B inhibitor; MC = multicentered; MD = mean difference; mg = milligrams; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NI = non-inferiority; NMS = neuroleptic malignant syndrome; NMSS = Non-motor Symptoms Scale; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; PC = placebo controlled; PD = Parkinson's Disease; PDSS = Parkinson's Disease Sleep Scale; PO = orally; PP = per protocol; QHS = at bedtime; RCT = randomized controlled trial; SD = standard deviation; TEAE = treatment-emergent adverse effects; TESAE = treatment-emergent serious adverse effects; tx = treatment; UPDRS = Unified Parkinson Disease Rating Scale; y = years.

NEW DRUG EVALUATION:

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
A sublingual (SL) film formulation of apomorphine was developed to address the practical limitations of subcutaneous apomorphine for on-demand, "rescue" treatment of individual "off" episodes. The SL film is designed to be placed under the tongue and deliver apomorphine systemically through absorption from the oral cavity mucosa, thus bypassing extensive first-pass metabolism associated with gastrointestinal administration of the drug.[15]

The efficacy of apomorphine SL for the acute, intermittent treatment of "off" episodes in patients with PD was established in one randomized, double-blind, placebo-controlled, multi-centered, parallel-group study which included sites from 32 academic neurology centers in the U.S. and one in Canada.[15] The effectiveness of apomorphine SC for injection had previously been studied in 3 RCTs for the acute symptomatic treatment of the recurring "off" episodes associated with advanced PD.[43]

The study enrolled patients with a mean duration of PD of 9 years (range: 2 years to 22 years) who were HY Stage 3 or less in the "on" state.[15] The mean number of daily "off" episodes was 4 and the mean duration of "off" episodes was slightly over an hour in both groups.[15] The baseline mean MDS-UPDRS part 3 score was 43.[15] All patients enrolled were receiving concomitant levodopa at a stable dose (mean 1033 mg/day) for at least 4 weeks before screening.[15] The most commonly used concomitant PD medications in addition to levodopa were dopamine agonists (51%), MOABIs (41%), amantadine (21%), and other dopaminergic agents (8%).[15]

The study included an open-label apomorphine SL titration phase and a 12-week double-blind, placebo-controlled maintenance phase.[15] In the open-label titration phase, all patients were titrated at 5 mg increments from 10 mg up to a tolerable dose of apomorphine SL (maximum dose 35 mg) that achieved a full "on" response.[15] In the titration phase, 141 patients arrived at the study site in an "off" state having not taken their regular morning dose of carbidopa/levodopa or any other adjunctive PD medications, as well as having taken their last dose of carbidopa/levodopa and any other adjunctive PD medications no later than midnight the night before.[15] Patients who tolerated the apomorphine SL dose but did not adequately respond were asked to return to the clinic within 3 days and the dose was increased by 5 mg.[15] The titration process was continued up to a maximum dose of 35 mg or until a full "on" response was achieved as determined by the investigator and the patient.[15] Patients who achieved a full "on" state with a tolerable dose of apomorphine SL were then randomized in a blinded fashion to apomorphine SL or placebo in a 1:1 ratio.[15] Thirty-two patients discontinued the study during the titration phase, including 12 patients who did so because of adverse events.[15] In the double-blind maintenance phase, 109 patients were randomly assigned to receive apomorphine SL (n=54) or placebo (n=55).[15] The doses of apomorphine SL administered at randomization that resulted in a full "on" response during the titration phase were: 10 mg (18%), 15 mg (27%), 20 mg (21%), 25 mg (19%) 30 mg (8%) and 35 mg (6%).[15] Dose administration was permitted up to 5-times per day in the double-blind maintenance phase.[15]

The primary endpoint of the study was the mean change from pre-dose to 30 minutes post-dose in the MDS-UPDRS Part 3 (motor examination) at the week 12 visit (of note, MDS-UPDRS Part 3 was measured pre-dose, and at 15, 30, 45, 60, and 90 minutes post-dose).[15] The key secondary endpoint was the percentage of patients with a patient-rated full "on" response within 30 minutes at the week 12 visit.[15]

The change from pre-dose to 30 minutes post-dose in the MDS-UPDRS part 3 score at week 12 was greater in patients who received apomorphine SL (-11.1; 95% CI, -14.0 to -8.2) than in patients treated with placebo (-3.5; 95% CI, -6.1 to -0.9) by a least squares mean difference of -7.6 (95% CI, -11.5 to -3.7; p=0.002), which was statistically significant and met the estimated MCID threshold for part 3 of the MDS-UPDRS (see Background section).[15] The investigators found statistically significant differences between the responses in the two arms at all post-dose time measurements (15, 30, 45, 60, 75 and 90 minutes).[15]

The response rate for a full "on" response within 30 minutes at the week 12 visit was also greater in patients treated with apomorphine SL than in those treated with placebo (35% vs. 16%, respectively; OR 2.81; 95% CI, 1.04 to 7.64; p=0.043).[15] Apomorphine SL did not result in statistically significant differences from placebo in improvement in PGI-I at week 12, MDS-UPDRS Part 2 at week 12, or change in PDQ-39 summary index score at week 12.[15] More patients treated with apomorphine SL saw improvement in CGI-I scores at week 12 versus patients treated with placebo (41% vs. 20%, respectively; 95% CI not reported; p=0.027); however, it is unclear if the improvement was in CGI-I scores were clinically meaningful.[15]

The evidence for apomorphine SL is limited to a single trial of 144 patients. The primary endpoint of the study was established to determine the efficacy of apomorphine SL to achieve an "on" response within 30 minutes. The study met the primary endpoint, but some limitations to the trial should be noted. Only patients who were responsive to levodopa and achieved a full "on" response at a tolerable dose during the titration phase were enrolled in the double-blind maintenance phase. Thus, the study was filled with patients who had already responded to apomorphine SL treatment. The treatment effect for "off" episodes were artificially assessed in the clinic in a defined "off" state, although it is worth noting that patients kept diaries that recorded "off" time which were largely congruent with the clinic results for the 2 days prior to the clinic visit. In addition, the high early study discontinuation rate in patients treated with apomorphine SL compared with those treated with placebo might increase risk of attrition bias and affect efficacy outcomes. Lastly, the drug sponsor funded the study and was responsible for data collection, monitoring, and statistical analysis. Details of the study, including risk of bias and applicability, are detailed in **Table 11**.

Clinical Safety:
During the titration phase with apomorphine SL, 58% of patients had at least one TEAE (see **Table 9**), which led to study discontinuation in 12% of patients.[15] During the double-blind maintenance phase, 89% of patients treated with apomorphine SL had at least one TEAE, compared with 45% of patients who received placebo.[15] During the double-blind maintenance phase, the TEAEs that resulted in early study discontinuation in the apomorphine SL arm were lip swelling, oral mucosal erythema, oropharyngeal swelling, delusion, disorientation, facial swelling, fall, fatigue, gingival edema, irritable bowel syndrome, lip edema, lip ulceration, mouth edema, nausea, vomiting, oral allergy syndrome, oropharyngeal pain, pharyngeal erythema, rhinorrhea, somnolence, swollen tongue, tongue polyp, and urticaria.[15]

Treatment-emergent adverse events led to early study discontinuation in 28% of patients treated with apomorphine SL and in 9% of those treated with placebo.[15] Oropharyngeal adverse events occurred in 31% of patients treated with apomorphine SL and were the most common type of adverse event that led to study discontinuation in the double-blind maintenance phase of the trial (17%).[15] A summary of TEAEs, including oropharyngeal-related TEAEs, is found in **Table 9**. Adverse events commonly attributed to dopamine-agonists, such as nausea, somnolence and dizziness, were more common in patient treated with apomorphine SL than placebo, but were infrequently associated with study discontinuation.[15] Nausea was reported more frequently in the apomorphine SL arm (28%) than the placebo arm (4%) despite provision of antiemetic therapy during the trial (excluding 5HT3 antagonists).[15] During the double-blind maintenance phase, orthostatic hypotension, hallucinations, and QT interval prolongation occurred in one patient each who received apomorphine SL.[15] However, no patients in the apomorphine SL arm experienced syncope, worsening dyskinesia, or an impulse control disorder.[15] No clinically meaningful differences were found in vital signs, electrocardiograms, or laboratory parameters.[15]

Table 9. Summary of Adverse Events in Phase 3 Apomorphine SL Trial.[15]

TEAEs in >5% of Patients in the OL Titration Phase		TEAEs in >5% of Patients in the DB Maintenance Phase			TEAEs Related to Oropharyngeal Disorders in ≥2% of Patients in the DB Maintenance Phase		
	APO		APO	PBO		APO	PBO
Any	58%	Any	89%	45%	Oral Mucosal Erythema	7%	4%
Nausea	21%	Nausea	28%	4%	Dry Mouth	6%	-
Yawning	12%	Somnolence	13%	2%	Glossodynia	4%	-
Dizziness	11%	Dizziness	9%	-	Lip Edema	4%	-
Somnolence	11%	Fatigue	7%	-	Lip Swelling	4%	-
Headache	8%	Oral Mucosal Erythema	7%	4%	Oropharyngeal Swelling	4%	-
Rhinorrhea	6%	Rhinorrhea	7%	-	Throat irritation	4%	-
Chills	6%	Vomiting	7%	-			
		Dry Mouth	6%	-			
		Fall	6%	2%			
		Headache	6%	-			
		Hyperhidrosis	6%	4%			
		Lacerations	6%	-			

Abbreviations: APO = apomorphine SL; DB = double-blind; OL = open-label; PBO = placebo; TEAE = treatment-emergent adverse event

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

Table 10. Pharmacology and Pharmacokinetic Properties.[44]

Parameter	
Mechanism of Action	• A non-ergoline dopamine agonist with high *in vitro* binding affinity for the dopamine D_4 receptor, and moderate affinity for the dopamine D_2, D_3, and D_5, and adrenergic α_1D, α_2B, α_2C receptors. • The precise mechanism of action as a treatment for "off" episodes is unknown, although it is believed to be due to stimulation of post-synaptic dopamine D_2-type receptors within the caudate-putamen in the brain.
Oral Bioavailability	• T_{max} 0.5-1 hour
Distribution and Protein Binding	• Vd/F = 3630 L • Protein binding not reported.
Half-Life	• $T_{1/2}$ = 1.7 h (range 0.8 to 3 h) • The apparent clearance of apomorphine does not appear to be influenced by age, gender, race, weight, duration of PD, levodopa dose, use of antiemetic, or duration of therapy. • No differences in apomorphine exposure were noted after administration of the SL formulation in patients with mild renal impairment (CLcr of ≥60 mL/min and <90 mL/min) versus patients with normal renal function (CLcr of ≥ 90 mL/min). Studies have not been conducted in patients with moderate to severe renal impairment.
Metabolism	• The major metabolic pathways for SL apomorphine are sulfation by multiple sulfotransferase (SULT) enzymes; glucuronidation by multiple glycosyltransferase (UGT) enzymes; N-demethylation catalyzed by multiple enzymes, including CYP2B6, CYP2C8, and CYP3A4/5; followed by conjugation. • Metabolism of apomorphine SL results in 3 major inactive metabolites: apomorphine sulfate, apomorphine glucuronide, and norapomorphine glucuronide.

Abbreviations: C_{max} = maximum concentration; h = hours; L = liters; PD = Parkinson's Disease; SL = sublingual; $t_{1/2}$ = half-life; T_{max} = time to reach the maximum concentration; Vd/F = apparent volume of distribution.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Motor symptoms (e.g., bradykinesia, rigidity, resting tremor)
2) Non-motor symptoms (e.g., autonomic, psychiatric and cognitive impairment)
3) Function (disability and impairment)
4) Health-related quality of life (e.g., PDQ-39)
5) Serious adverse events

Primary Study Endpoint:

1) Motor symptoms, as assessed by Δ MDS-UPDRS part 3 (pre-dose to 30 minutes post-dose)

Table 11. Comparative Evidence Table for Apomorphine Sublingual Film.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. DB, PC, RCT, MC 12 weeks 6002-US-005	1. apomorphine SL mg/d 2. placebo 1:1 OL titration period: Titration started at 10 mg, which could be increased on subsequent days in 5 mg increments to a max of 35 mg until full ON response achieved within 45 min of administration w/o intolerable AE.	Demographics: -Mean age: 62.7 y -Male: 62% -White: 93% -MDS-UPDRS part 3 (pre-dose): 43.1 -HY ON score 2 or 2.5: 83% -OFF episodes/day: 3.9 -Mean L-dopa dose: 1033 mg/d -Dopa agonist: 56% Key Inclusion Criteria: -Age ≥18 y -Idiopathic PD -Responsive to L-dopa w/ DCI but w/ early AM OFF episodes -Stable doses of L-dopa administered QID or more. -OFF time ≥2 h/day -HY Stage 3 or less in ON state -MMSE >25 Key Exclusion Criteria: -Atypical or Secondary PD -Previous neurological procedure for PD, continuous SC apomorphine infusion, or Duodopa/Duopa	ITT: 1. 54 2. 55 PP: 1. 34 2. 46 Attrition: 1. 37% 2. 16%	Primary Endpoint: Δ MDS-UPDRS part 3 from pre-dose to 30 min post-dose (at week 12 visit): 1. -11.1 2. -3.5 LSMD -7.6 (95% CI, -11.5 to -3.7) Secondary Endpoints: % w/ self-rated full ON response within 30 min (at week 12 visit): 1. 35% 2. 16% OR 2.81 (95% CI, 1.04 to 7.64) Improved PGI-I (baseline to week 12): 1. 37% 2. 20% (1 vs. 2, p=0.062, CI NR) Improved CGI-I (baseline to week 12): 1. 41% 2. 20% (1 vs. 2, p=0.027, CI NR) Δ PDQ-39 (baseline to week 12): 1. 0.309 2. -1.671 MD 1.979 (95% CI, -2.162 to 6.120)	 NA 19%/6 NS 21%/5 NS	TEAE (OL titration): 82/141 (58%) TEAE (DB RCT): 1. 89% 2. 45% Nausea (OL titration): 29/141 (21%) Nausea (DB RCT): 1. 28% 2. 4% Somnolence (OL titration): 16/141 (11%) Somnolence (DB RCT): 1. 13% 2. 2% Dizziness (OL titration): 16/141 (11%) Dizziness (DB RCT): 1. 9% 2. 0% OL Titration Discontinuation from TEAE: 9/141 (9%) DB RCT Discontinuation from TEAE: 1. 28% 2. 9%	 NA 44%/NA NA 24%/NA NA 11%/NA NA 9%/NA NA 19%/NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized by interactive web-response system, was not stratified; block size was 4. Computer-generated random allocation use corresponded with the sequentially numbered foil pouches of study medication. However, the small number of participants led to unequal demographic characteristics between groups in gender and HY stages. Performance Bias: (unclear) all patients and study personnel were masked to treatment assignments; active and placebo study medication and packaging identical in size, shape, color and appearance. However, patients assigned to placebo after OL titration period w/ apomorphine likely unmasked treatment arms. Detection Bias: (high) efficacy assessments performed at the clinic in patients in a practically defined OFF state at week 0, 4, 8, and 12. Assessment included part 3 of the MDS-UPDRS (motor exam) done pre-dose and at 15, 30, 45, 60 and 90 min post-dose. Patients self-administered study drug at home for treatment of up to 5 OFF episodes per day. A diary was kept for the 2 days prior to the clinic visit to determine whether full ON response was achieved at 30 min post-dose. Anti-nausea medication was administered for 3 days before initiation of titration in OL phase and could be continued during DL maintenance phase. Unknown if data assessors were blinded to treatment. Attrition Bias: (high) Very high attrition rate for apomorphine arm; analysis of endpoints based on mITT (patients who received at least one post-randomization dose). Missing data imputed using LOCF. Reporting Bias: (low) endpoints reported as designed in methodology, but some CI NR.

		-Current 5HT3 antagonist*, dopamine antagonist** or dopamine depleting agent -Major psychiatric disorder -Drug or alcohol dependency -H/o hallucinations or ICD -Dementia						Other Bias: (high) study funded by drug sponsors Cynapsus Therapeutics and Sunovion, and who were responsible for data collection, monitoring and statistical analyses. **Applicability**: Patient: 32% of enrolled participants d/c'd OL titration phase limiting DB phase to patients who could achieve full ON response to apomorphine at a tolerable dose. Intervention: patients received the medication in a defined OFF state (anti-PD medication withheld overnight for ~12h); trained staff administered medication and patients were specifically instructed not to swallow for 3 min (apomorphine is rapidly sulfonated in the stomach and not absorbed). Patients were maintained on their standard anti-PD medication regimen. Doses that resulted in full ON response during titration phase were: 10 mg (18%), 15 mg (27%), 20 mg (21%), 25 mg (19%), 30 mg (8%), 35 mg (6%). Comparator: placebo appropriate to establish efficacy of the SL formulation. Outcomes: A full ON response was defined as an ON response similar to that obtained with L-dopa; time to medication effect was 21 min. Setting: 32 academic neurology centers in the U.S. and one in Canada.

Abbreviations: AM = morning; ARR = absolute risk reduction; CGI-I = Clinical Global Impressions – Improvement in illness scale; CI = confidence interval; d = days; DB = double blind; DCI = decarboxylase inhibitor (e.g., carbidopa); GI = gastrointestinal; H/o = history of; HY = Hoehn & Yale scale; ICD = impulse control disorder; ITT = intention to treat; L-dopa = levodopa; LOCF = last observation carried forward; LSM = least-square mean; LSMD = least-square mean difference; MC = multicentered; mg = milligrams; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; mITT = modified intention to treat; MMSE = Mini-Mental State Examination; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; OL = open label; OR = odds ratio; PC = placebo controlled; PD = Parkinson's Disease; PDQ-39 = Parkinson's Disease Questionnaire; PGI-I = Patient Global Impression – Improvement Scale; PP = per protocol; QID = 4-times daily; RCT = randomized controlled trial; SC = subcutaneous; SD = standard deviation; TEAE = treatment-emergent adverse effects; TESAE = treatment-emergent serious adverse effects; UPDRS = Unified Parkinson Disease Rating Scale; y = years.
*ie, ondansetron, granisetron, dolasetron, palonosetron, alosetron
**excluding quetiapine or clozapine

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
benztropine mesylate	BENZTROPINE MESYLATE	TABLET	ORAL	Y
carbidopa/levodopa	CARBIDOPA/LEVODOPA	TABLET	ORAL	Y
carbidopa/levodopa	SINEMET 10-100	TABLET	ORAL	Y
carbidopa/levodopa	SINEMET 25-100	TABLET	ORAL	Y
carbidopa/levodopa	SINEMET 25-250	TABLET	ORAL	Y
carbidopa/levodopa	CARBIDOPA-LEVODOPA ER	TABLET ER	ORAL	Y
carbidopa/levodopa	SINEMET CR	TABLET ER	ORAL	Y
carbidopa/levodopa/entacapone	CARBIDOPA-LEVODOPA-ENTACAPONE	TABLET	ORAL	Y
carbidopa/levodopa/entacapone	STALEVO 100	TABLET	ORAL	Y
carbidopa/levodopa/entacapone	STALEVO 125	TABLET	ORAL	Y
carbidopa/levodopa/entacapone	STALEVO 150	TABLET	ORAL	Y
carbidopa/levodopa/entacapone	STALEVO 200	TABLET	ORAL	Y
carbidopa/levodopa/entacapone	STALEVO 50	TABLET	ORAL	Y
carbidopa/levodopa/entacapone	STALEVO 75	TABLET	ORAL	Y
entacapone	COMTAN	TABLET	ORAL	Y
entacapone	ENTACAPONE	TABLET	ORAL	Y
pramipexole di-HCl	MIRAPEX	TABLET	ORAL	Y
pramipexole di-HCl	PRAMIPEXOLE DIHYDROCHLORIDE	TABLET	ORAL	Y
selegiline HCl	SELEGILINE HCL	CAPSULE	ORAL	Y
trihexyphenidyl HCl	TRIHEXYPHENIDYL HCL	ELIXIR	ORAL	Y
trihexyphenidyl HCl	TRIHEXYPHENIDYL HCL	TABLET	ORAL	Y
amantadine HCl	GOCOVRI	CAP ER 24H	ORAL	N
amantadine HCl	AMANTADINE	CAPSULE	ORAL	N
amantadine HCl	AMANTADINE	SOLUTION	ORAL	N
amantadine HCl	OSMOLEX ER	TAB BP 24H	ORAL	N
amantadine HCl	AMANTADINE	TABLET	ORAL	N
bromocriptine mesylate	BROMOCRIPTINE MESYLATE	CAPSULE	ORAL	N
bromocriptine mesylate	PARLODEL	CAPSULE	ORAL	N
bromocriptine mesylate	BROMOCRIPTINE MESYLATE	TABLET	ORAL	N
bromocriptine mesylate	PARLODEL	TABLET	ORAL	N
carbidopa	CARBIDOPA	TABLET	ORAL	N
carbidopa	LODOSYN	TABLET	ORAL	N
carbidopa/levodopa	RYTARY	CAPSULE ER	ORAL	N
carbidopa/levodopa	DUOPA	INT PMP SP	MISCELL	N
carbidopa/levodopa	CARBIDOPA-LEVODOPA	TAB RAPDIS	ORAL	N
levodopa	INBRIJA	CAP W/DEV	INHALATION	N
levodopa	INBRIJA	CAPSULE	INHALATION	N

levodopa	LARODOPA	TABLET	ORAL	N
pramipexole di-HCl	MIRAPEX ER	TAB ER 24H	ORAL	N
pramipexole di-HCl	PRAMIPEXOLE ER	TAB ER 24H	ORAL	N
rasagiline mesylate	AZILECT	TABLET	ORAL	N
rasagiline mesylate	RASAGILINE MESYLATE	TABLET	ORAL	N
ropinirole HCl	REQUIP XL	TAB ER 24H	ORAL	N
ropinirole HCl	ROPINIROLE ER	TAB ER 24H	ORAL	N
ropinirole HCl	REQUIP	TABLET	ORAL	N
ropinirole HCl	ROPINIROLE HCL	TABLET	ORAL	N
rotigotine	NEUPRO	PATCH TD24	TRANSDERM	N
safinamide mesylate	XADAGO	TABLET	ORAL	N
selegiline HCl	ZELAPAR	TAB RAPDIS	ORAL	N
selegiline HCl	SELEGILINE HCL	TABLET	ORAL	N
tolcapone	TASMAR	TABLET	ORAL	N
tolcapone	TOLCAPONE	TABLET	ORAL	N

Appendix 2: Abstracts of Comparative Clinical Trials

Lee J-Y, Jeon B, Koh S-B, et al. Behavioural and trait changes in parkinsonian patients with impulse control disorder after switching from dopamine agonist to levodopa therapy: results of REIN-PD trial. *J Neurol Neurosurg Psychiatry*. 2019; 90:30–37.

Objective: In this multicentre open-label trial, we compared behavioural and neuropsychiatric symptoms in Parkinson's disease (PD) patients with impulse control disorders (ICD) treated with dopamine agonists before and 12 weeks after substituting dopamine agonists with an equivalent dose of levodopa/carbidopa slow-release formulation.
Methods: Baseline characteristics of 50 PD patients with ICD were compared with those of 60 medicated and 40 drug-naïve PD control groups. Neuropsychiatric trait changes in the pD-IcD group were investigated 12 weeks after the intervention. ICD behaviours were assessed via modified Minnesota Impulsive Disorders Interview (mMIDI), whereas parkinsonian severity and neuropsychiatric characters were systematically assessed with the Unified PD Rating Scale (UPDRS) and a predefined neuropsychological assessment battery. Results at baseline, ICD patients showed higher scores in the Neuropsychiatric Inventory and anxiety, anger and obsessive-compulsive traits compared with both PD control groups. In contrast, the three PD groups showed indifference in the impulsivity scales. At 12 weeks post intervention, ICD behaviours significantly improved ($p<0.001$, Δ modified MIDI score = −5.27 ± 5.75) along with the UPDRS II daily activity scores ($p=0.02$, Δ = −2.07 ± 4.53). Behavioural disinhibition tended to improve ($p=0.06$), although no significant changes were observed in the Neuropsychiatric Inventory and personality trait scores. Dopamine agonist withdrawal syndrome developed in 5.3% of the PD-ICD group.
Conclusions: This study provides class IV evidence suggesting that switching from dopamine agonists to levodopa/carbidopa slow-release formulations alleviated ICD behaviours in PD patients leading to improvement in daily activities whereas neuropsychiatric traits associated with ICD persisted after the 12-week therapy.

Trenkwalder C, Kuoppamaki M, Vahterito M, et al. Increased dose of carbidopa with levodopa and entacapone improves "off" time in a randomized trial. *Neurology*. 2019; 92:1487-1496.

Objective: To investigate whether increased fixed carbidopa doses of 65 or 105 mg (ODM-101/65 and ODM-101/105) in combination with 75, 100, 125, or 150 mg of levodopa and 200 mg of entacapone might improve "off" time in fluctuating Parkinson disease (PD) compared to the standard combination of 4:1 levodopa/carbidopa with the usual 200 mg of entacapone (LCE) during a 4-week treatment period.
Methods: This was a randomized, double-blind, double-dummy, active-controlled, crossover, multicenter, phase II, proof-of-concept study in patients with fluctuating PD.
Results: One hundred seventeen patients were randomized into the study (mean age 67.0 years; daily "off" time 5.3 hours; mean daily levodopa dose 610 mg). Carryover-adjusted mean changes from baseline "off " times were during ODM-101/65, −1.53 hours ($p = 0.02$ vs LCE), during ODM-101/105, −1.57 hours ($p = 0.01$ vs LCE), and during LCE −0.91 hours. Changes in daily "on" time without dyskinesia were 1.54 hours ($p = 0.005$ vs LCE), 1.38 hours ($p = 0.0214$ vs LCE), and 0.69 hours, respectively. Changes in "on" time with troublesome dyskinesia were <0.1 hours and not significantly different between treatments. In patients with high-activity COMT genotypes Val/Met or Val/Val, "off " time was reduced more with ODM-101/65 and ODM-101/105 than with LCE ($p = 0.015$ and $p = 0.006$). No difference between the treatments was seen in safety and tolerability. The most common treatment-related adverse effects were nausea, dizziness, drug-effect decrease, and dyskinesia, which were in most cases mild or moderate in severity. Treatment-related serious adverse events were diarrhea (ODM-101/105 and LCE), and myocardial ischemia and blood creatine kinase increase (LCE).
Conclusion: Increasing the dose of carbidopa in combination with levodopa and entacapone should be considered in the treatment of fluctuating PD to improve daily "off " times. Genotyping patients with PD according to COMT activity may improve individual treatment strategies.

Verschuur CVM, Suwijn SR, Boel JA, et al. Randomized delayed-start trial of levodopa in Parkinson's disease. *N Engl J Med*. 2019; 380:315-324.

Background: Levodopa is the main treatment for symptoms of Parkinson's disease. Determining whether levodopa also has a disease-modifying effect could provide guidance as to when in the course of the disease the treatment with this drug should be initiated.
Methods: In a multicenter, double-blind, placebo-controlled, delayed-start trial, we randomly assigned patients with early Parkinson's disease to receive levodopa (100 mg three times per day) in combination with carbidopa (25 mg three times per day) for 80 weeks (early-start group) or placebo for 40 weeks followed by levodopa in combination with carbidopa for 40 weeks (delayed-start group). The primary outcome was the between-group difference in the mean change from baseline to week 80 in the total score on the Unified Parkinson's Disease Rating Scale (UPDRS; scores range from 0 to 176, with higher scores signifying more severe disease). Secondary analyses included the progression of symptoms, as measured by the UPDRS score, between weeks 4 and 40 and the noninferiority of early initiation of treatment to delayed initiation between weeks 44 and 80, with a noninferiority margin of 0.055 points per week.
Results: A total of 445 patients were randomly assigned: 222 to the early-start group and 223 to the delayed-start group. The mean (±SD) UPDRS score at baseline was 28.1 ±11.4 points in the early-start group and 29.3 ±12.1 points in the delayed-start group. The change in UPDRS score from baseline to week 80 was −1.0 ±13.1 points and −2.0 ±13.0 points, respectively (difference, 1.0 point; 95% confidence interval [CI], −1.5 to 3.5; P=0.44); this finding of no significant between-group difference at week 80 implies that levodopa had no disease-modifying effect. Between weeks 4 and 40, the rate of progression of symptoms, as measured in UPDRS points per week, was 0.04 ±0.23 in the early-start group and 0.06 ±0.34 in the delayed-start group (difference, −0.02; 95% CI, −0.07 to 0.03). The corresponding rates between weeks 44 and 80 were 0.10 ±0.25 and 0.03 ±0.28 (difference, 0.07; two-sided 90% CI, 0.03 to 0.10); the difference in the rate of progression between weeks 44 and 80 did not meet the criterion for noninferiority of early receipt of levodopa to delayed receipt. The rates of dyskinesia and levodopa-related fluctuations in motor response did not differ significantly between the two groups.
Conclusions: Among patients with early Parkinson's disease who were evaluated over the course of 80 weeks, treatment with levodopa in combination with carbidopa had no disease-modifying effect.

Appendix 3: Medline Search Strategy

1 exp Benztropine/ 694
2 exp Levodopa/ 16074
3 entacapone.mp. 648
4 exp Pramipexole/ 949
5 exp Selegiline/ 2335
6 exp Trihexyphenidyl/ 912
7 exp Amantadine/ 5841
8 exp Bromocriptine/ 6950
9 exp Carbidopa/ 2342
10 rasagiline.mp. 659
11 ropinirole.mp. 921
12 rotigotine.mp. 552
13 safinamide.mp. 159
14 exp Tolcapone/ 331
15 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 34154
16 limit 15 to (english language and humans and yr="2018 -Current" and (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review") and "humans only (removes records about animals)") 132

Appendix 4: Prescribing Information Highlights

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

NOURIANZ™ (istradefylline) tablets, for oral use
Initial U.S. Approval: 2019

----------INDICATIONS AND USAGE----------
NOURIANZ is an adenosine receptor antagonist indicated as adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing "off" episodes (1).

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage is 20 mg orally once daily. The dosage may be increased to a maximum of 40 mg once daily (2.1).
- May be taken with or without food (2.1).
- Patients with hepatic impairment: Maximum recommended dosage with moderate hepatic impairment is 20 mg once daily; use of NOURIANZ in patients with severe hepatic impairment should be avoided (2.4, 8.7).
- Patients who smoke 20 or more cigarettes per day (or the equivalent of another tobacco product): Recommended dosage is 40 mg once daily (2.5, 8.8).

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 20 mg and 40 mg (3).

----------CONTRAINDICATIONS----------
None (4).

----------WARNINGS AND PRECAUTIONS----------
- Dyskinesia: Monitor patients for dyskinesia or exacerbation of existing dyskinesia (5.1).
- Hallucinations / Psychotic Behavior: Consider dosage reduction or stopping NOURIANZ if occurs (5.2).
- Impulse Control / Compulsive Behaviors: Consider dosage reduction or stopping NOURIANZ if occurs (5.3).

----------ADVERSE REACTIONS----------
The most common adverse reactions (at least 5% and more frequent than placebo) were dyskinesia, dizziness, constipation, nausea, hallucination, and insomnia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Kyowa Kirin Inc. at 1-844-768-3544 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong CYP 3A4 inhibitors: Recommended maximum dosage with concomitant use is 20 mg once daily (2.2, 7.1).
- Strong CYP 3A4 inducers: Avoid use (2.3, 7.1).

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

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

Revised: 8/2019

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

ONGENTYS (opicapone) capsules, for oral use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------
ONGENTYS is a catechol-O-methyltransferase (COMT) inhibitor indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes. (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage is 50 mg administered orally once daily at bedtime. (2.1)
- Patients should not eat food for 1 hour before and for at least 1 hour after intake of ONGENTYS. (2.1)
- The recommended dosage in patients with moderate hepatic impairment is 25 mg orally once daily at bedtime; avoid use in patients with severe hepatic impairment. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 25 mg and 50 mg. (3)

----------CONTRAINDICATIONS----------
- Concomitant use of non-selective monoamine oxidase (MAO) inhibitors. (4)
- History of pheochromocytoma, paraganglioma, or other catecholamine secreting neoplasms. (4)

----------WARNINGS AND PRECAUTIONS----------
- Cardiovascular Effects with Concomitant Use of Drugs Metabolized by Catechol-O-Methyltransferase (COMT): May cause arrhythmias, increased heart rate, and excessive changes in blood pressure. Monitor patients when treated concomitantly with products metabolized by COMT. (4, 5.1)
- Falling Asleep During Activities of Daily Living: Advise patients prior to treatment. (5.2)
- Hypotension/Syncope: If occurs, consider discontinuing ONGENTYS or adjusting dosage of other medications that can lower blood pressure. (5.3)
- Dyskinesia: May cause or exacerbate dyskinesia; consider levodopa or dopaminergic medication dose reduction. (5.4)
- Hallucinations and Psychosis: Consider stopping ONGENTYS if occurs. (5.5)
- Impulse Control/Compulsive Disorders: Consider stopping ONGENTYS if occurs. (5.6)
- Withdrawal-Emergent Hyperpyrexia and Confusion: When discontinuing ONGENTYS, monitor patients and consider adjustment of other dopaminergic therapies as needed. (5.7)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥4% and > placebo): dyskinesia, constipation, blood creatine kinase increased, hypotension/syncope, and weight decreased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Neurocrine Biosciences, Inc. at 877-641-3461 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Avoid use in patients with end-stage renal disease. (8.6)

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

Revised: 4/2020

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

KYNMOBI™ (apomorphine hydrochloride) sublingual film
Initial U.S. Approval: 2004

INDICATIONS AND USAGE

KYNMOBI is a non-ergoline dopamine agonist indicated for the acute, intermittent treatment of "off" episodes in patients with Parkinson's disease (1)

DOSAGE AND ADMINISTRATION

- For sublingual administration only (2.1)
- Dose initiation should be supervised by a healthcare provider (2.1, 2.3)
- Treatment with a concomitant antiemetic, e.g. trimethobenzamide, is recommended, beginning 3 days prior to initial dose of KYNMOBI (2.1, 5.1)
- The dose range for KYNMOBI is 10 mg to 30 mg per dose, administered sublingually, as needed (2.2)
- KYNMOBI doses should be separated by at least 2 hours (2.2)
- Maximum of 5 doses per day; maximum single dose is 30 mg (2.2, 2.3)

DOSAGE FORMS AND STRENGTHS

KYNMOBI sublingual film: 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg of apomorphine hydrochloride (3, 16)

CONTRAINDICATIONS

- Concomitant use of KYNMOBI with 5HT3 antagonists (4)
- Hypersensitivity to apomorphine or any of its ingredients including sodium metabisulfite (4)

WARNINGS AND PRECAUTIONS

- Nausea and vomiting may occur (2.1, 5.1)
- Falling asleep during activities of daily living and daytime somnolence may occur, discontinue KYNMOBI if occurs (5.2)
- Syncope and hypotension/orthostatic hypotension may occur, monitor blood pressure (5.3)
- Oral mucosal irritation may occur, which may require pausing or discontinuing treatment (5.4)
- Falls may occur, or increase (5.6)
- May cause hallucinations and psychotic-like behavior (5.7)
- May cause impulse control and impulsive behaviors; consider dose reduction or discontinuing KYNMOBI if occurs (5.8)
- Withdrawal-emergent hyperpyrexia and confusion may occur with rapid dose reduction or withdrawal (5.9)
- May prolong QTc and cause torsades de pointes or sudden death; consider risk factors prior to initiation (5.10)

ADVERSE REACTIONS

Most common adverse reactions (incidence at least 10% in patients treated with KYNMOBI and with an incidence greater than placebo) were nausea, oral/pharyngeal soft tissue swelling, oral/pharyngeal soft tissue pain and paraesthesia, dizziness, and somnolence (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sunovion Pharmaceuticals Inc. at 1-877-737-7226 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Concomitant use of antihypertensive medications and vasodilators may increase risk for hypotension, myocardial infarction, falls and injuries (7.2)
- Dopamine antagonists may diminish the effectiveness of KYNMOBI (7.4)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1)

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

Revised: 5/2020

Appendix 5: Key Inclusion Criteria

Population	Patients with Parkinson's disease diagnosis
Intervention	FDA-approved pharmacological agent
Comparator	FDA-approved pharmacological agent(s)
Outcomes	Mortality, morbidity, quality of life, functioning or symptoms
Timing	Multiple days
Setting	Outpatient management

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, istradefylline, opicapone, or apomorphine SL film?	**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: *10/20 (AG); 3/18; 7/16; 9/14; 9/13; 09/10*
Implementation: *TBD; 4/16/18; 8/16, 1/1/14, 1/1/11*