# PDL DRUG REVIEW

**Proprietary Name: Ongentys®**
**Common Name: opicapone**
**PDL Category: Parkinsons COMT Inhibitors**

| Comparable Products | Preferred Drug List Status |
|---|---|
| Nourianz | Non-Preferred |

## Summary


**Pharmacology/Usage:** Opicapone, the active ingredient of Ongentys®, is a peripheral, selective, and reversible catechol-O-methyltransferase (COMT) inhibitor. COMT catalyzes the transfer of the methyl group of S-adenosyl-L-methionine to the phenolic group of substrates that contain a catechol structure. Physiological substrates of COMT include catecholamines (dopamine, norepinephrine, and epinephrine) and their hydroxylated metabolites. When decarboxylation of levodopa is prevented by carbidopa, COMT becomes the major metabolizing enzyme for levodopa, catalyzing its metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD).

**Indication:** As adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing 'off' episodes

There is no pregnancy category for this product; however, the risk summary indicates that there are no adequate data on the developmental risk associated with use in pregnant women. In animal studies, oral administration of opicapone during pregnancy resulted in adverse effects on embryofetal development at clinically relevant plasma exposures. The safety and efficacy of use in the pediatric population have not been established.

**Dosage Form:** Capsules: 25mg, 50mg

**Recommended Dosage:** Take 50mg PO QHS. Patients should not eat food for 1 hour before and at least 1 hour after intake of Ongentys®.

Dose adjustments are not required with mild, moderate, or severe renal impairment; however, avoid the use in patients with end-stage renal disease (ESRD). Due to a potential for increased exposure, monitor patients with severe renal impairment for adverse reactions and discontinue Ongentys® if tolerability issues arise. Dose adjustments are not required with mild hepatic impairment. In patients with moderate hepatic impairment, the recommended dose is 25mg PO QHS. Avoid the use of Ongentys® in patients with severe hepatic impairment.

**Drug Interactions:** Both Ongentys® and non-selective MAO inhibitors (e.g. phenelzine, isocarboxazid, and tranylcypromine) inhibit catecholamine metabolism, leading to increased levels of catecholamines. Concomitant use may increase the risk of possible arrhythmias, increased heart rate, and excessive changes in blood pressure. Concomitant use of Ongentys® with non-selective MAO inhibitors is contraindicated. Selective MAO-B inhibitors can be used concomitantly with Ongentys®.

Concomitant use of Ongentys® with drugs metabolized by COMT may affect the pharmacokinetics of those drugs, which may increase the risk of possible arrhythmias, increased heart rate, and excessive changes in blood pressure. Drugs known to be metabolized by COMT should be administered with caution. Monitor for changes in heart rate, rhythm, and blood pressure if use Ongentys® concomitantly with drugs metabolized by COMT.

**Box Warning:** There is no box warning listed with this product.

**Common Adverse Drug Reactions:** *Listed % incidence for adverse drug reactions= reported % incidence for drug (Ongentys®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included dyskinesia (14%), dizziness (2%), constipation (4%), dry mouth (2%), hallucination (2%), insomnia (1%), blood creatine kinase increased (3%), weight decreased (4%), hypotension/syncope (4%), and hypertension (1%).

As discussed in the drug interactions section, possible arrhythmias, increased heart rate, and excessive changes in blood pressure may occur with concomitant use of Ongentys® and drugs metabolized by COMT, regardless of the route of administration. Monitor patients treated concomitantly with Ongentys® and drugs metabolized by COMT.

Patients treated with dopaminergic medications and medications that increase levodopa exposure, including Ongentys®, have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles. Before starting treatment with Ongentys®, advise patients of the potential to develop drowsiness and ask about factors that may increase the risk for somnolence with dopaminergic therapy. Consider discontinuing Ongentys® or adjusting other dopaminergic or sedating medications if a patient develops daytime sleepiness or episodes of falling asleep during activities that require full attention.

Hypotension, syncope, and presyncope occurred in 5% of patients treated with Ongentys® vs 1% with placebo. Monitor patients for hypotension.

Ongentys® potentiates the effects of levodopa and may cause dyskinesia or exacerbate pre-existing dyskinesia. Reducing the patient's daily levodopa dosage or the dosage of another dopaminergic drug may mitigate dyskinesia that occurs during treatment with Ongentys®.

Hallucinations occurred in 3% of patients treated with Ongentys vs 1% of patients treated with placebo. Delusions, agitation, or aggressive behavior occurred in 1% of the Ongentys® group vs none in the placebo group. Consider stopping Ongentys® if hallucinations or psychotic-like behaviors occur. Patients with a major psychotic disorder should ordinarily not be treated with Ongentys® due to the risk of exacerbating the psychosis with an increase in central dopaminergic tone.

Patients treated with Ongentys® can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges while taking one or more dopaminergic therapies that increase central dopaminergic tone. In some cases, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. In 2 studies, impulse control disorders occurred in 1% of patients treated with Ongentys® as compared with none treated with placebo. Reassess the patient's current therapies for Parkinson's disease and consider stopping Ongentys® if a patient develops such urges while taking Ongentys®.

A symptom complex resembling neuroleptic malignant syndrome, with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in drugs that increase central dopaminergic tone. In controlled studies of Ongentys®, patients discontinued Ongentys® treatment without dose tapering or gradual withdrawal. There were no reports of neuroleptic malignant syndrome in Ongentys® controlled clinical trials. When discontinuing Ongentys®, monitor patients and consider adjustment of other dopaminergic therapies as needed.

**Contraindications:** In patients with:

- Concomitant use of non-selective monoamine oxidase inhibitors

- Pheochromocytoma, paraganglioma, or other catecholamine secreting neoplasms

**Manufacturer:** Neurocrine Biosciences, Inc

**Analysis:** The efficacy of Ongentys® for the adjunctive treatment to levodopa/carbidopa in patients with PD experiencing 'off' episodes was assessed in two double-blind, randomized, parallel-group studies of 14 to 15 weeks in duration, with study 1 being placebo- and active-controlled and study 2 being placebo-controlled.

Study 1 (N=600) included patients randomized to treatment with one of 3 doses of Ongentys®, active-control, or placebo. Data regarding the active comparator was not found in the prescribing information. This study included adults with a mean age of 64 years, while 60% were male and all patients were Caucasian. The mean duration of PD was 7 years for the Ongentys® group compared to 7.7 years for the placebo group, with mean onset of motor fluctuations of 2.2 years prior to study enrollment. Furthermore, 82% of patients in both groups used concomitant PD medications in addition to levodopa. The most commonly used were dopamine agonists (68%), amantadine (23%), MAO-B inhibitors (20%), and anticholinergics (5%).

The primary efficacy endpoint of this study was the change in mean absolute OFF-time based on 24-hour patient diaries completed 3 days prior to each of the scheduled visits. Results suggested that Ongentys® 50mg significantly reduced mean absolute OFF-time compared to placebo. Results can be seen in the table below, which was adapted from the prescribing information.

| Treatment | N | Baseline mean | LS mean change from baseline | Placebo-subtracted difference | Adjusted p-value |
|---|---|---|---|---|---|
| Placebo | 120 | 6.17 hours | -0.93 | - | - |
| Ongentys® 50mg | 115 | 6.20 hours | -1.95 | -1.01 | p=0.002 |

In addition, ON-time without troublesome dyskinesia was a secondary endpoint. Results can be seen in the table below, which was adapted from the prescribing information.

| Treatment | N | Baseline mean | LS mean change from baseline | Placebo-subtracted difference | Nominal p-value |
|---|---|---|---|---|---|
| Placebo | 120 | 9.61 | 0.75 | - | - |
| Ongentys® 50mg | 115 | 9.54 | 1.84 | 1.08 | p=0.001 |

Study 2 (N=427) included patients randomized to treatment with either one of two doses of Ongentys® or placebo. This study included patients with a mean age of 66 years in the Ongentys® group and 62 years in the placebo group, while most were male (61% Ongentys® vs 53% placebo) and Caucasian (78% Ongentys® vs 66% placebo). The mean duration of PD at baseline across treatment groups was 8.2 years and the mean onset of motor fluctuations was 3.2 years prior to study enrollment. In addition, 85% of patients treated with Ongentys® compared to 81% of patients treated with placebo used concomitant PD medications in addition to levodopa. The most commonly used were dopamine agonists (70%), amantadine (21%), MAO-B inhibitors (20%), and anticholinergics (12%).

The primary efficacy endpoint was the change in mean absolute OFF-time based on 24-hour patient diaries completed 3 days prior to each of the scheduled visits. Results suggested that Ongentys® 50mg significantly reduced mean absolute OFF-time compared to placebo. Results can be seen in the table below, which was adapted from the prescribing information.

| Treatment | N | Baseline mean | LS mean change from baseline | Placebo-subtracted difference | Adjusted p-value |
|---|---|---|---|---|---|
| Placebo | 135 | 6.12 hours | -1.07 | - | - |
| Ongentys® 50mg | 147 | 6.32 hours | -1.98 | -0.91 | p=0.008 |

ON-time without troublesome dyskinesia was a secondary efficacy endpoint. Results can be seen in the table below, which was adapted from the prescribing information. This endpoint was not statistically significantly different.

| Treatment | N | Baseline mean | LS mean change from baseline | Placebo-subtracted difference | Nominal p-value |
|---|---|---|---|---|---|
| Placebo | 135 | 9.61 hours | 0.80 | - | - |
| Ongentys® 50mg | 147 | 9.37 hours | 1.43 | 0.62 | p=0.065 |

**Place in Therapy:** Ongentys® is a peripheral, selective, and reversible COMT inhibitor indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing 'off' episodes. It is the first and only once-daily COMT inhibitor with this indication. Concomitant use of non-selective MAO inhibitors with Ongentys® is contraindicated. In two phase 3 studies, Ongentys® significantly reduced mean absolute OFF-time as compared with placebo. In addition, both studies assessed ON-time without troublesome dyskinesia as a secondary efficacy endpoint. Only study 1 reported statistically significantly differences with Ongentys® compared with placebo, while results from study 2 were not statistically significant between Ongentys® and placebo.

In addition, study 1 included an active comparator. In the full-text study by Ferreira[2], adults were randomized to Ongentys® and placebo as well as entacapone (200mg with every levodopa intake; N=120). The primary endpoint of the least-squares mean change from baseline in absolute time in the off state was -1.605 in the entacapone group. Opicapone 50mg was superior to placebo and non-inferior to entacapone. Entacapone was also superior to placebo. In addition, the % of patients with a reduction of ≥1 hour in time in the off state was 70% with Ongentys® 50mg and 58% with entacapone 200mg, which was not significantly different (p=0.063). For the placebo group, the % of patients was 48%. Opicapone was significantly different from placebo (p=0.001) but entacapone was not significantly different from placebo (p=0.094).

Ongentys® is effective in reducing the symptoms of off periods in Parkinson's patients. It is therefore recommended that Ongentys® be added to the Preferred Drug List as preferred.

**PDL Placement:** ☒ **Preferred**
☐ **Non-Preferred**

## References

[1] Ongentys [package insert]. San Diego, CA: Neurocrine Biosciences, Inc; 2020.
[2] Ferreira JJ, Lees A, Rocha JF, et al. Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomized, double-blind, controlled trial. *Lancet Neurol*. 2016; 15(2): 154-165.