Ongentys® (opicapone) capsules

OPTIMIZE LEVODOPA WITH ONGENTYS[1,2]

Increased levodopa exposure by up to 74%,
helping more levodopa be available to reach the brain[1,2]

Started to reduce off time as early as 1 week,
with reductions of 2 hours vs. 1 hour with placebo seen at 14/15 weeks—studied through 1 year[2]

No titration required—one capsule, taken at bedtime[1]
— Patients should not eat food for 1 hour before and at least 1 hour after taking ONGENTYS® (opicapone) capsules[1]

Important Information

INDICATION & USAGE

ONGENTYS is indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

ONGENTYS is contraindicated in patients with:

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

Please see full Important Safety Information on pages 14-15.
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IS YOUR LEVODOPA/CARBIDOPA STRATEGY MISSING SOMETHING?

Before levodopa can get to the brain, 2 major enzymes may metabolize it substantially: DDC and COMT[3-9]

- When the DDC enzyme is inhibited by carbidopa, COMT becomes the predominant peripheral metabolic pathway for levodopa[4,7,8,10-12]

THE EARLY LEVODOPA/CARBIDOPA PARTNER FOR OFF TIME THAT OPTIMIZES LEVODOPA[1,2]

A unique molecule in COMT inhibition, ONGENTYS has[1,2,13]

High COMT-binding affinity

Prolonged pharmacologic effect

Once-daily dosing

- As carbidopa protects levodopa from the DDC enzyme, ONGENTYS® (opicapone) capsules protects levodopa from the COMT enzyme in the periphery[1,13]
  - Distinct from MAO-B inhibitors and dopamine agonists, which don't directly impact levodopa before it reaches the brain[1,14-16]

COMT=catechol-O-methyltransferase; DDC=dopa decarboxylase; MAO=monoamine oxidase.

IMPORTANT SAFETY INFORMATION (CONT'D)
WARNINGS & PRECAUTIONS

Cardiovascular Effects with Concomitant Use of Drugs Metabolized by Catechol-O-Methyltransferase (COMT) - 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 (including inhalation). Monitor patients treated concomitantly with ONGENTYS and drugs metabolized by COMT.

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ONGENTYS INCREASED LEVODOPA TROUGH CONCENTRATIONS AND OVERALL LEVODOPA EXPOSURE, RESULTING IN SMOOTHER PEAK-TO-TROUGH VARIATIONS[1,2,17]

Patients taking levodopa/carbidopa every 4 hours experienced

Up to

74%

increase in total levodopa exposure which may lead to more levodopa to reach the brain[1,2]

Decreased levodopa variations by

46%*

110% increase in levodopa trough concentrations while increasing peak concentrations by only 35%, helping maintain smoother peak-to-trough variations[2,17]

STUDY DESIGN: A randomized, open-label, Phase 1 study to assess the pharmacokinetics and pharmacodynamics of repeated doses of ONGENTYS 50 mg administered orally as adjunctive therapy to stable levodopa/carbidopa in patients with PD (N=16). Patients were randomized to receive immediate-release levodopa/carbidopa either every 3 hours (Q3H, n=7) or every 4 hours (Q4H, n=9). All patients received once-daily ONGENTYS 50 mg in the evening from days 1 to 14. Data for Q3H includes 100% trough concentration increase and 38% peak concentration increase.[2]

*Peak-to-trough variations were calculated as: $([C_{max} - C_{min}]/C_{ave})x100$.[2]

IMPORTANT SAFETY INFORMATION (CONT'D)
WARNINGS & PRECAUTIONS

Falling Asleep During Activities of Daily Living and Somnolence - Patients have reported falling asleep while engaged in activities of daily living, including driving, which may result in accidents. Consider discontinuing ONGENTYS or adjusting other dopaminergic/sedating medications. Advise patients to avoid driving and other potentially dangerous activities.

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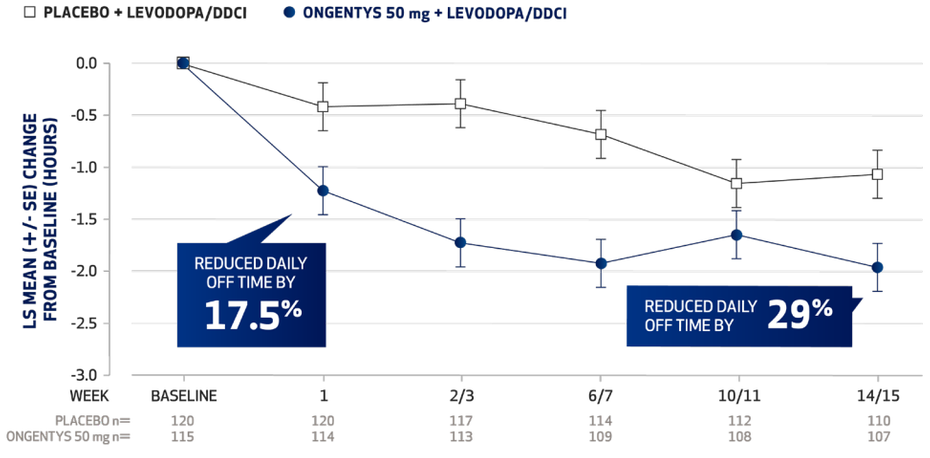
Ongentys® (opicapone) capsules

SIGNIFICANT REDUCTIONS IN DAILY OFF TIME AT 14/15 WEEKS WITH A REDUCTION SEEN AS EARLY AS 1 WEEK[1,2]

Once-daily ONGENTYS® (opicapone) capsules **significantly reduced off time** by 1.95 hours compared to 0.93 hours with placebo at Week 14/15[1*]

REDUCED DAILY OFF TIME[1,2†] — STUDY 1



*P=0.002, adjusted P value was calculated using a gatekeeping procedure controlling for multiplicity.[1]

†82% of patients in both groups were also taking concomitant PD medications in addition to levodopa DDCI, including dopamine agonists (68%), amantadine (23%), MAO-B inhibitors (20%), and anticholinergics (5%).[1]

DDCI=dopa decarboxylase inhibitor; LS=least squares; MAO=monoamine oxidase; SE=standard error.

STUDY DESIGN: ONGENTYS was studied in two 14- to 15-week, double-blind, randomized, parallel-group studies of patients with PD experiencing off episodes being treated with levodopa/DDCI (alone or in combination with other PD medications). The double-blind period for each study began with an up to 3-week levodopa/DDCI adjustment period, followed by a stable maintenance period of 12 weeks. The primary endpoint of both studies was mean change in off time, based on 24-hour patient diaries completed 3 days prior to each of the scheduled visits. After the double-blind period, patients were able to enroll in a 1-year open-label extension of ONGENTYS.[1,2]

IMPORTANT SAFETY INFORMATION (CONT'D)
WARNINGS & PRECAUTIONS

Hypotension/Syncope - Monitor patients for hypotension and advise patients about the risk for syncope. If necessary, consider discontinuing ONGENTYS or adjusting the dosage of other medications that can lower blood pressure.

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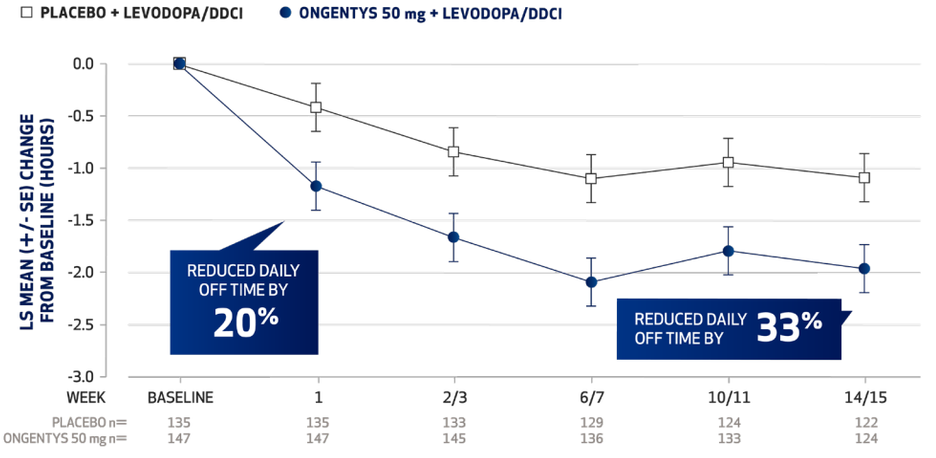
Once-daily ONGENTYS **significantly reduced off time** by 1.98 hours compared to 1.07 hours with placebo at Week 14/15[1*]

REDUCED DAILY OFF TIME[1,2†] — STUDY 2



*P=0.008, adjusted P value was calculated using Dunnett's alpha level adjustment to control for multiplicity.[1]

†85% of patients taking ONGENTYS and 81% of patients taking placebo were also taking concomitant PD medications in addition to levodopa/DDCI, including dopamine agonists (70%), amantadine (21%), MAO-B inhibitors (20%), and anticholinergics (12%).[1]

Started to reduce off time as early as 1 week[2‡]

‡For Study 1: -1.24 hours vs -0.42 hours for placebo; for Study 2: -1.22 hours vs -0.47 hours for placebo.

IMPORTANT SAFETY INFORMATION (CONT'D)
WARNINGS & PRECAUTIONS

Dyskinesia - ONGENTYS may cause or exacerbate dyskinesia. Consider levodopa or dopaminergic medication dose reduction.

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Ongentys® (opicapone) capsules

IN THE EARLIER STAGES OF LEVODOPA TREATMENT AND DISEASE STATE, ONGENTYS REDUCED OFF TIME[18,19]

The following subgroups saw an improvement in off time vs placebo in post-hoc analyses[18]*:

Earlier disease state subgroups

- H&Y <2.5 subgroup
- Onset of motor fluctuations of ≤2 years

Earlier levodopa subgroups

- Levodopa/DDCI intakes 3 times daily
- <500 mg/daily levodopa DDCI
- Levodopa/DDCI monotherapy

*In the post-hoc analysis of two phase 3 trials, BIPARK 1 and BIPARK 2, patients were evaluated in earlier stages of both their disease course and levodopa treatment pathway.[18]

Since these results are from post-hoc analyses, treatment effects were not prespecified and not adequately powered to examine differences; and thus, limitations should be carefully considered in interpreting these results.

DDCI=dopa decarboxylase inhibitor; H&Y=Hoehn and Yahr.

PLEASE SEE STUDY DESIGN ON PAGE 4

IMPORTANT SAFETY INFORMATION (CONT'D)
WARNINGS & PRECAUTIONS

Hallucinations and Psychosis - Consider stopping ONGENTYS® (opicapone) capsules if these occur. Patients with a major psychotic disorder should ordinarily not be treated with ONGENTYS.

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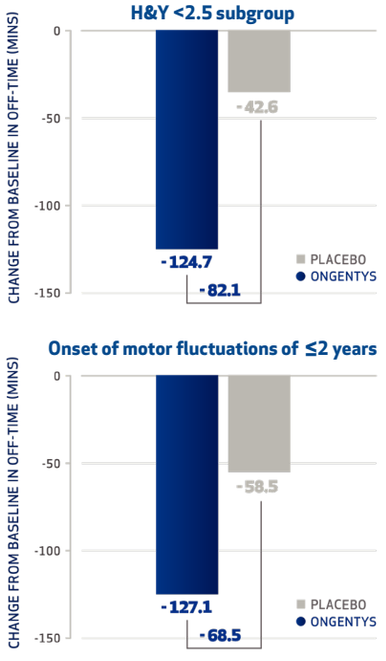
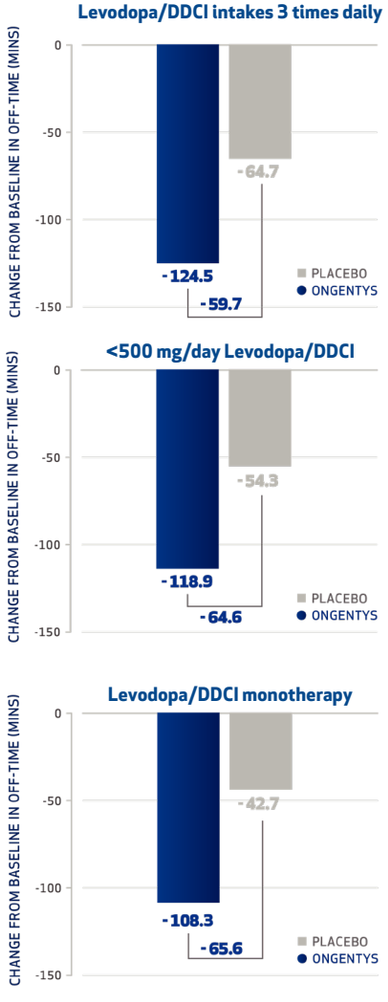
Earlier Stage Subgroups Post-Hoc Analyses[18]



H&Y=Hoehn and Yahr.

Earlier Levodopa Subgroups Post-Hoc Analyses[18]



IMPORTANT SAFETY INFORMATION (CONT'D)
WARNINGS & PRECAUTIONS

Impulse Control/Compulsive Disorders - Patients may experience intense urges (eg, gambling, sexual, spending money, binge eating) and the inability to control them. It is important for prescribers to ask about the development of new or increased urges. Monitor for occurrence of intense urges and consider discontinuing ONGENTYS® (opicapone) capsules if they occur.

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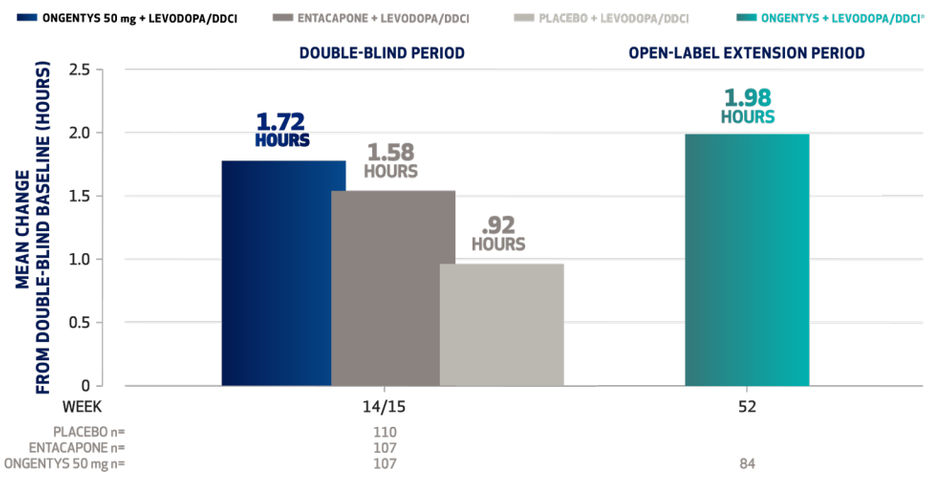
Ongentys® (opicapone) capsules

INCREASED GOOD ON TIME —SUSTAINED THROUGH 1 YEAR[2]

INCREASED GOOD ON TIME IN THE 1-YEAR OPEN-LABEL EXTENSIONS OF THE DOUBLE-BLIND STUDIES[2] STUDY 1



In the open-label period, patients who switched from entacapone to ONGENTYS® (opicapone) capsules had almost 45 minutes additional increase in good on time [2]

~91% of patients who completed the double-blind study (N=542) chose to enroll in the 1-year open-label extension period—with **~87% staying on through the end of 1 year.**[2]

A mean 2.00-hour reduction in daily off time from double-blind baseline was seen for ONGENTYS® (opicapone) capsules (N=98) at Week 52.[2]*

*Includes patients who were on ONGENTYS 50 mg in the double-blind period and continued on ONGENTYS in the open-label extension with dosing per the study design.[2]

DDCI=dopa decarboxylase inhibitor.

STUDY DESIGN: Two 14- to 15-week, double-blind, randomized, parallel-group studies of patients with PD experiencing off episodes being treated with levodopa/DDCI (alone or in combination with other PD medications). The double-blind period for each study began with an up to 3-week levodopa/DDCI adjustment period, followed by a stable maintenance period of 12 weeks.

In Study 1, patients (N=600) were randomized to treatment with 1 of 3 doses of ONGENTYS. The intent-to-treat population included patients treated with ONGENTYS 50 mg (n=115), placebo (n=120), or active comparator (entacapone) (n=120). In Study 2, patients (N=427) were

Please see full Important Safety Information on pages 14-15.
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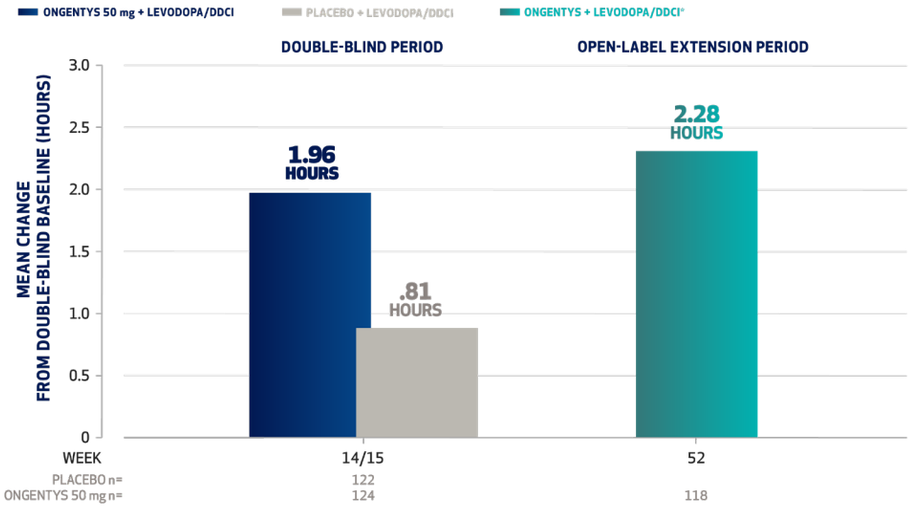
INCREASED GOOD ON TIME IN THE 1-YEAR OPEN-LABEL EXTENSIONS OF THE DOUBLE-BLIND STUDIES[2] STUDY 2



~98% of patients who completed the double-blind study (N=376) chose to enroll in the 1-year open-label extension period—with **~78% staying on through the end of 1 year.**[2]

A mean 2.64-hour reduction in daily off time from double-blind baseline was seen for ONGENTYS® (opicapone) capsules (N=118) at Week 52.[2†]

*Includes patients who were on ONGENTYS 50 mg in the double-blind period and continued on ONGENTYS in the open-label extension with dosing per the study design.[2]
†Post-hoc analyses. Good on time data from the open-label extension period is presented (based on pre-specified Last Observation Carried Forward analysis approach) broken down by visit by dose.[2]

STUDY DESIGN (CONT'D): randomized to treatment with either 1 of 2 doses of ONGENTYS or placebo. The intent-to-treat population included patients treated with ONGENTYS 50 mg (n=147) or placebo (n=135). The primary endpoint of both studies was mean change in off time, based on 24-hour patient diaries completed 3 days prior to each of the scheduled visits. A secondary endpoint was mean change in good on time (defined as on time without troublesome dyskinesia), as recorded in patients' Hauser diaries.

After the double-blind period, patients were able to enroll in a 1-year open-label extension of ONGENTYS. Patients who had been on placebo or active comparator in the double-blind period received ONGENTYS in the open-label period, starting at 25 mg and up-titrating to 50 mg if "wearing off" is not sufficiently controlled. If unacceptable dopaminergic AEs appeared, the levodopa/DDCI dose should be adjusted first and only then, if not sufficient, the ONGENTYS dose can be down-titrated. In Study 1, ~91% of patients who completed the double-blind period (N=542) chose to enroll, and in Study 2, ~98% of patients who completed the double-blind period (N=376) chose to enroll. For the majority of the extension period, investigators were able to adjust patients' levodopa/DDCI according to clinical response.[1,2]

Please see full Important Safety Information on pages 14-15.
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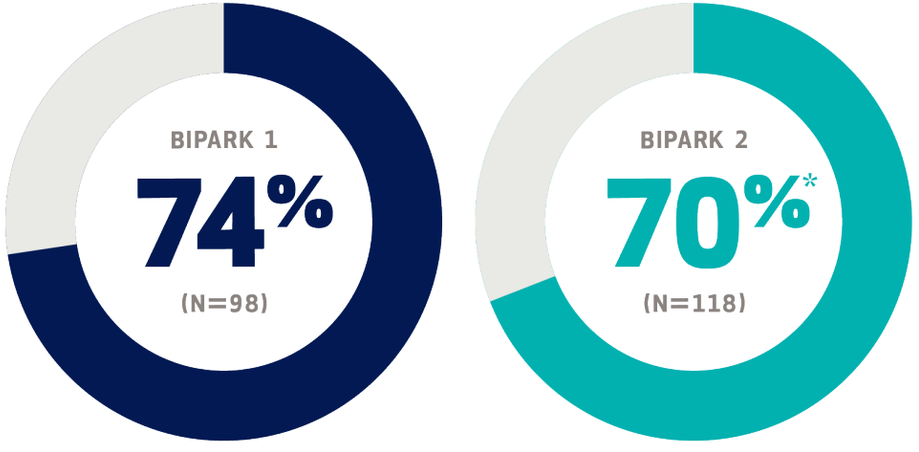
Ongentys® (opicapone) capsules

ONGENTYS HELPED MAINTAIN LEVODOPA/ DDCI DOSING IN BOTH CLINICAL TRIALS AND REAL WORLD STUDIES[20,21]

In clinical trials, the majority of patients taking ONGENTYS® (opicapone) capsules were able to continue on the same dose of levodopa/DDCI through 1 year[2]



In a real-world study, introducing ONGENTYS helped 85% of patients maintain their levodopa dose after 3 months of treatment (N=393).[20†]

*Post-hoc analyses. Maintained levodopa/DDCI dosing data from the open-label extension period (based on pre-specified Last Observation Carried forward analysis approach).[2]

†OPTIPARK was a prospective, open-label, single-arm, multicenter trial evaluating ONGENTYS 50 mg effectiveness in levodopa treated PD patients experiencing motor fluctuations.[20]

DDCI=dopa decarboxylase inhibitor.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS & PRECAUTIONS

Withdrawal-Emergent Hyperpyrexia and Confusion - A symptom complex resembling neuroleptic malignant syndrome can develop with rapid dose reduction or withdrawal of drugs that increase central dopaminergic tone. When discontinuing ONGENTYS, monitor patients and consider adjustment of dopaminergic therapies as needed.

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GENERALLY WELL TOLERATED IN CLINICAL STUDIES[1]

In the pooled analysis of 2 double-blind studies

ADVERSE REACTIONS IN STUDY 1 AND STUDY 2 (INCIDENCE OF ≥2% IN PATIENTS TAKING ONGENTYS AND >PLACEBO)[1]

ADVERSE REACTION	PLACEBO (N=257) %	ONGENTYS 50 MG (N=265) %
Dyskinesia	6	20
Dizziness	1	3
Constipation	2	6
Dry mouth	1	3
Hallucination*	1	3
Insomnia	2	3
Blood creatine kinase increased	2	5
Weight decreased	0	4
Hypotension/syncope†	1	5
Hypertension	2	3

*Includes hallucinations, hallucinations visual, hallucinations auditory, and hallucinations mixed.[1]
†Includes hypotension, orthostatic hypotension, syncope, and presyncope.[1]

ONGENTYS can be used with most concomitant PD treatments[1‡§]

‡Concomitant use of ONGENTYS with non-selective MAO inhibitors (eg, phenelzine, isocarboxazid, and tranylcypromine) is contraindicated.[1]
§ONGENTYS can be taken concomitantly with selective MAO-B inhibitors used to treat PD (eg, rasagiline and selegiline).[1]

MAO=monoamine oxidase.

IMPORTANT SAFETY INFORMATION (CONT'D)

ADVERSE REACTIONS

The most common adverse reactions (incidence at least 4% and greater than placebo) were dyskinesia, constipation, blood creatine kinase increased, hypotension/syncope, and weight decreased.

You are encouraged to report negative side effects of prescription drugs to the FDA.

Visit MedWatch at **www.fda.gov/medwatch** or call 1-800-FDA-1088.

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Ongentys® (opicapone) capsules

A SIMPLE ONCE-DAILY CAPSULE—NO TITRATION REQUIRED[1]

50-mg standard dose—no need for titration[1]

- Patients with moderate hepatic impairment should use a 25-mg capsule, as the mean overall plasma exposure of ONGENTYS® (opicapone) capsules increased in these patients[1,2]*

Taken once-daily at bedtime[1]

- Bedtime dosing may enable minimal disruption to patients' daily routines[1,2]

Works with patients' existing levodopa/DDCI dosing regimens[2]

- Patients can start ONGENTYS without having to change their current levodopa/DDCI regimens—and ONGENTYS was studied with many levodopa/DDCI formulations[2]
- Most patients in clinical studies were able to maintain stable levodopa/DDCI dosing through 1 year[2]

Do not take with food[1]

- Patients should not eat food for 1 hour before and at least 1 hour after taking ONGENTYS[1]
- Food reduces absorption. When ONGENTYS was taken with a moderate-fat/moderate-calorie meal, its mean peak plasma concentration decreased by 62% and its mean overall exposure decreased by 31%[1]

*ONGENTYS has not been studied in patients with severe hepatic impairment. Avoid use in these patients.[1]

DDCI=dopa decarboxylase inhibitor.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS

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- Pheochromocytoma, paraganglioma, or other catecholamine secreting neoplasms.

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IN CLINICAL STUDIES, MOST DYSKINESIA EVENTS WERE MILD TO MODERATE[22-24]

Understanding discontinuation rates across a pooled analysis of 2 double-blind studies

- Discontinuation rates for the double-blind period due to adverse events were 8% for patients taking ONGENTYS® (opicapone) capsules and 6% for patients taking placebo[1]
- The most common adverse reaction leading to discontinuation was dyskinesia, reported in 3% of patients taking ONGENTYS and 0.4% of patients taking placebo[1]
- After the initial 2- to 3-week levodopa/DDCI adjustment period, dyskinesia rates were 8.3% for ONGENTYS and 1.6% for placebo[2]

Because ONGENTYS optimizes levodopa, it may mean that you need to adjust your patient's dose and/or frequency of levodopa if they're experiencing dyskinesia[1]

IMPORTANT SAFETY INFORMATION (CONT'D)
WARNINGS & PRECAUTIONS

Cardiovascular Effects with Concomitant Use of Drugs Metabolized by Catechol-O-Methyltransferase (COMT) - 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 (including inhalation). Monitor patients treated concomitantly with ONGENTYS and drugs metabolized by COMT.

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Ongentys® (opicapone) capsules

Important Information

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Ongentys® (opicapone) capsules

IMPORTANT SAFETY INFORMATION (CONT'D)

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You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch at www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see accompanying ONGENTYS full Prescribing Information.

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