CLINICAL UPDATE

Brand Name	Ongentys®
Generic Name	opicapone
Drug Manufacturer	Neurocrine Biosciences, Inc

Clinical Update

TYPE OF CLINICAL UPDATE

New Strength (25 mg)

FDA APPROVAL DATE

April 24, 2020

LAUNCH DATE

January 19, 2021

REVIEW DESIGNATION

Standard

TYPE OF REVIEW

New Drug Application (NDA): 212489

DISPENSING RESTRICTIONS

Open Distribution

Overview

INDICATION(S) FOR USE

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.

MECHANISMS OF ACTION

Opicapone is a selective and reversible inhibitor of catechol-O-methyltransferase (COMT). 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 DOPA, 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).

DOSAGE FORM(S) AND STRENGTH(S)

Capsules: 25 mg and 50 mg

DOSE & ADMINISTRATION

- The recommended dosage is 50 mg administered orally once daily at bedtime.
- Patients should not eat food for 1 hour before and for at least 1 hour after intake of Ongentys®.
- 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.

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EFFICACY

The efficacy of Ongentys® for the adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes was evaluated in two double-blind, randomized, parallel-group, placebo- and active-controlled (Study 1, NCT01568073), or placebo-controlled (Study 2, NCT01227655) studies of 14–15-week duration. All patients were treated with levodopa/DOPA decarboxylase inhibitor (DDCI) (alone or in combination with other PD medications). The double-blind period for each study began with a period for levodopa/DDCI dose adjustment (up to 3 weeks), followed by a stable maintenance period of 12 weeks.

Study 1

In Study 1, patients (n=600) were randomized to treatment with one of 3 doses of Ongentys®. The intention to treat (ITT) population included patients treated with Ongentys® 50 mg once daily (n=115) or placebo 10 Reference ID: 4597703 (n=120). Baseline demographic characteristics were similar across all treatment groups: approximately 60% of patients were male, mean age was 64 years, and all patients were Caucasian. Baseline PD characteristics in the treatment groups were mean duration of PD of 7 years for Ongentys® 50 mg compared to 7.7 years for placebo, and mean onset of motor fluctuations of 2.2 years prior to study enrollment. Eighty-two percent 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 was the change in mean absolute OFF-time based on 24-hour patient diaries completed 3 days prior to each of the scheduled visits. Ongentys® 50 mg significantly reduced mean absolute OFF-time compared to placebo.

Table 1: Study 1 - Absolute OFF-time (Hours) Change from Baseline to Endpoint

	N	Baseline Mean (SE)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference (95% CI)	Adjusted p-value [a]
Placebo	120	6.17 hours (0.162)	-0.93 (0.223)	--	--
ONGENTYS 50 mg	115	6.20 hours (0.166)	-1.95 (0.233)	-1.01 (-1.620, -0.407)	p=0.002

CI=confidence interval; LS =least squares; N=total number of patients; SE=standard error.
[a] Adjusted p values were calculated using a gatekeeping procedure controlling for multiplicity.

Table 2: Study 2 - Absolute ON-time Without Troublesome Dyskinesia (Hours) Change from Baseline to Endpoint

	N	Baseline Mean (SE)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference (95% CI)	Nominal p-value [a]
Placebo	120	9.61 (0.191)	0.75 (0.237)	--	--
ONGENTYS 50 mg	115	9.54 (0.183)	1.84 (0.247)	1.08 (0.440, 1.728)	p=0.001

CI=confidence interval; LS =least squares; N=total number of patients; SE=standard error.
[a] Unadjusted p-value.

Study 2: In Study 2, patients (n=427) were randomized to treatment with either one of two doses of Ongentys® once daily (n=283) or placebo (n=144). The intention to treat (ITT) study population included patients treated with

Ongentys® 50 mg once daily (n=147) or placebo (n=135). Baseline demographic characteristics (Ongentys® 50 mg vs. placebo) were: mean age (66 years vs. 62 years), male (61% vs. 53%), Caucasian (78% vs. 66%) and Asian (21% vs. 31%). Baseline PD characteristics were generally similar across treatment groups with a mean duration of PD of 8.2 years, and a mean onset of motor fluctuations of 3.2 years prior to study enrollment. Eighty-five percent of patients treated with Ongentys® 50 mg compared to 81% of patients who received 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. Ongentys® 50 mg significantly reduced mean absolute OFF-time compared to placebo.

Table 3: Study 2 - Absolute OFF-time (Hours) Change from Baseline to Endpoint

	N	Baseline Mean (SE)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference (95% CI)	Adjusted p-value [a]
Placebo	135	6.12 (0.200)	-1.07 (0.239)	--	--
ONGENTYS 50 mg	147	6.32 (0.183)	-1.98 (0.230)	-0.91 (-1.523, -0.287)	p=0.008

CI=confidence interval; LS =least squares; N=total number of patients; SE=standard error.
[a] Adjusted p values were calculated using Dunnett's alpha level adjustment to control for multiplicity.

Table 4: Study 2 - Absolute ON-time without troublesome dyskinesia (Hours) Change from Baseline to Endpoint

	N	Baseline Mean (SE)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference (95% CI)	Nominal p-value
Placebo	135	9.61 (0.206)	0.80 (0.256)	--	--
ONGENTYS 50 mg	147	9.37 (0.183)	1.43 (0.247)	0.62 (-0.039, 1.287)	p=0.065 (NS*)

CI=confidence interval; LS =least squares; N=total number of patients; SE=standard error.
*= not statistically significant.