RXADVANCE
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NEW DRUG APPROVAL

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

New Drug Approval

FDA Approval Date: April 24, 2020

Review Designation: Type 1 - New Molecular Entity

Type of Review: New Drug Application (NDA): 212489

Dispensing restriction: None

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

The most complete pathologic analysis of Parkinson's disease and the clear delineation of the brain stem lesions was performed in 1953 by Greenfield and Bosanquet. As far as statistics go, PD is the second most common neurodegenerative disease after Alzheimer disease. The population prevalence of PD increases from about 1% at age 60 to 4% by age 80.

There are approximately 1 million individuals living with PD in the United States in 2020 and approximately 60,000 Americans are diagnosed with the disease each year. This number increases to approximately 10 million people worldwide who are living with the disease. Men are 1.5 times more likely to have PD than women.

The estimated cost of the disease is approximately $52 billion per year in the United States, with medications costing approximately $2500 per year and therapeutic surgery costing approximately $100,000 per person. Symptoms for these patients may include tremor, weakness, spasticity, visual disturbances, bradykinesia, loss of automatic movements, and speech and writing changes.

In PD, certain nerve cells in the brain start to break down gradually and die due to a lack of dopamine. The causes of this disease are unknown, but genomics may play a role, such as having a family member affected by it. Triggers may include exposure to certain toxins or environmental factors.

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.

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 (n=120). 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.

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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).

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.

	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
Absolute ON-time Without Troublesome Dyskinesia (Hours) Change from Baseline to					
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
Absolute OFF-time (Hours) Change from Baseline to Endpoint					
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
Absolute ON-time without troublesome dyskinesia (Hours) Change from Baseline to					
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.					

Safety

ADVERSE EVENTS

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

WARNINGS & 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.
- Falling Asleep During Activities of Daily Living: Advise patients prior to treatment.
- Hypotension/Syncope: If occurs, consider discontinuing Ongentys® or adjusting dosage of other medications that can lower blood pressure.
- Dyskinesia: May cause or exacerbate dyskinesia; consider levodopa or dopaminergic medication dose reduction.
- Hallucinations and Psychosis: Consider stopping Ongentys® if occurs.
- Impulse Control/Compulsive Disorders: Consider stopping Ongentys® if occurs.
- Withdrawal-Emergent Hyperpyrexia and Confusion: When discontinuing Ongentys®, monitor patients and consider adjustment of other dopaminergic therapies as needed.

CONTRAINDICATIONS

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

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Clinical Pharmacology

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.

Dose & Administration

ADULTS

The recommended dosage of Ongentys® 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®.

PEDIATRICS

Safety and effectiveness in pediatric patients have not been established.

GERIATRICS

No dose adjustment is required for elderly patients. Of the total number of patients who received Ongentys® 50 mg in Study 1 and Study 2, 52% of patients were 65 years and older. No overall differences in safety and effectiveness were observed between these patients and younger patients, but greater sensitivity to adverse reactions of some older individuals cannot be ruled out.

RENAL IMPAIRMENT

The renal route of elimination plays a minor role in the clearance of opicapone. Avoid use of Ongentys® in patients with end-stage renal disease (ESRD) (CLcr <15 mL/min). No dosage adjustment is required for patients with mild, moderate, or severe renal impairment. However, because of a potential for increased exposure, monitor patients with severe renal impairment for adverse reactions and discontinue Ongentys® if tolerability issues arise.

HEPATIC IMPAIRMENT

In patients with moderate hepatic impairment (Child-Pugh B), the recommended dose of Ongentys® is 25 mg orally once daily at bedtime. Avoid use of Ongentys® in patients with severe (Child-Pugh C) hepatic impairment.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Capsules: 25 mg and 50 mg.