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Ongentys® (Opicapone): A Drug Lighting a New Path for Treatment of Parkinson's Disease

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Parkinson's Disease (PD) is a neurodegenerative disorder that predominantly affects the dopamine-producing neurons in a specific area of the brain called substantia nigra.[1] It is the second most common chronic, progressive, neurodegenerative disease, with a mean age of onset of around 60 years of age.[2] The cause of PD is thought to be multifactorial, involving both genetic and environmental factors. Common risk factors include age, ethnicity, and gender. Men were found to be more likely to develop PD, with the male-to-female ratio being approximately 3:2.3 Age is thought to be the greatest risk factor for development of PD; the incidence increases drastically with age and peaks after 80 years of age.[3] In regards to ethnicity, occurrence is highest in people of Hispanic ethnic origin, followed by non-Hispanic Whites, Asians, and Blacks.[4] Environmental factors that could potentially increase the risk of developing PD include pesticide exposure, prior head injury, rural living, beta-blocker use, and agricultural occupation.[5] Of these environmental risk factors, pesticide exposure had the strongest association with an increased risk for developing PD.[6] In terms of genetic risk factors, having a first-degree or any relative with PD could at least double the risk of PD. The greatest genetic risk factor of developing PD is a mutation in GBA, a protein involved in the metabolism of cholesterol.[3] There is a five-fold increased risk of developing PD in patients with a GBA mutation. Around 5 to 10 percent of patients with PD are estimated to carry a GBA mutation.[7] Other common genetic risk factors include LRRK2 for dominantly inherited PD and parkin for recessively inherited PD.[5]

Parkinson's Disease is thought to occur in phases. The prodromal (or premotor) phase characterizes the period before the onset of the classic motor symptoms.[2] This phase can include various non-motor features including psychiatric disorders, cognitive disorders, sleep abnormalities, and others. The prodromal phase can be prolonged, often lasting years before the onset of the classic motor symptoms. The early stage of PD starts with the occurrence of the motor symptoms, where additional non-motor features such as fatigue and mild cognitive impairment can occur. The late or advanced phase of PD is characterized by a worsening of motor features and the presence of postural instability, another motor feature associated with frequent falls and gait freezing. Urinary symptoms, dementia, and orthostatic hypotension are non-motor features common in the late or advanced stage of PD.[5]

This disease eventually results in a gradual loss of dopaminergic neurons in the substantia nigra which can lead to the three cardinal motor symptoms of PD called bradykinesia, rigidity, and rest tremor.[8] Diagnosis of PD requires at least two out of the three cardinal symptoms. At diagnosis, these symptoms are usually unilateral, but they gradually become bilateral as the disease progresses.[9] Even though there is no cure for PD, there are many options available for symptomatic treatment. The main goal of therapy is to restore dopamine receptor function to maintain the best possible quality of life. Typical classes of drugs used in PD include Monoamine Oxidase (MAO) inhibitors, Catechol O-Methyl Transferase (COMT) inhibitors, Dopamine receptor agonists, and anticholinergics. The 2017 National Institute for Health and Care Excellence (NICE) Guidelines for PD in adults recommends using levodopa, typically paired with carbidopa to prevent decarboxylation, as first line treatment in patients whose motor symptoms are affecting their quality of life whereas dopamine agonists, levodopa, or MAO inhibitors can be considered if their motor symptoms do not affect their quality of life.[10] A major issue with chronic use of levodopa is the wearing off phenomena, which leads to an increase in motor fluctuations called "off" episodes. Options to help decrease off episodes include MAO inhibitors or COMT inhibitors.[9]

Ongentys® (opicapone) is a new medication recently approved by the FDA on April 24th, 2020. It is indicated as an adjunctive treatment to levodopa/carbidopa in patients with PD experiencing an increase in the off-state. This article will review the safety and efficacy of opicapone for the treatment of PD.

IN THIS ISSUE

Pharmacology

Mechanism of Action

Opicapone is a third generation COMT inhibitor and is the first agent in its class approved for the treatment of off episodes as an adjunct to levodopa and carbidopa. Opicapone blocks the COMT enzyme, responsible for breaking down levodopa, making

more available to reach the brain by increasing its clinical effects and enabling patients to gain control over motor symptoms.[11]

Pharmacokinetics

Opicapone has been shown to have a linear, dose-dependent absorption in clinical trials.[12] It is important to note that mean plasma exposure (AUC) was decreased by 31% when opicapone was taken with a moderate fat/moderate caloric meal. Plasma protein binding is greater than 99% and the volume of distribution is about 30 L.[12] Opicapone's main metabolic pathway is through sulphonation. Other metabolic pathways include reduction, methylation, and glucuronidation. Furthermore, studies have shown that age, renal impairment, or race have no relevant clinical effects on Opicapone. Opicapone exhibits the lowest potential for cytotoxicity in comparison with other COMT inhibitors.[12]

Pharmacodynamics

A once-daily administration of 50 mg of opicapone helped to cause an inhibition of COMT activity. The maximum inhibition was 84% but was able to be maintained greater than 65% over a 24-hour period.[13] There is no concern regarding cardiac abnormalities associated with opicapone. At a dose 16 times the recommended dose, opicapone did not prolong the QT interval by any clinically relevant extent. Additionally, opicapone was able to significantly increase the effects of levodopa; the overall levodopa exposure was increased by 62-94% in PD patients following a once-daily administration of opicapone at bedtime with levodopa/carbidopa administered every three or four hours.

CLINICAL TRIALS

The FDA approved opicapone mainly based on two phase III trials named BIPARK-1 and BIPARK-2.[14,15] Both trials were randomized, double-blind, multinational, parallel group-controlled trials. They were developed to test the safety and efficacy of opicapone. Both studies lasted approximately 15 weeks. Another trial by Rocha JF et al that conducted two phase I studies aided in the decision to recommend a once daily administration of opicapone at bedtime.[16] Both BIPARK series used the Hoehn and Yahr scale to assess the progressions of PD for their inclusion/exclusion criteria. The Hoehn and Yahr includes five stages. Stage one is the earliest stage where symptoms are mild and usually only seen unilaterally. Stage two is where symptoms present bilaterally and may develop months or years after stage one. Stage three is defined by a loss of balance and movement slowness, but the patient is still fully independent. Stage four is where patient is noticeably incapacitated and unable to live independently but can still walk or stand without assistance. Stage five is the most advanced where the patient is restricted to a wheelchair or bed.[17] The following section will review the BIPARK series trials.

BIPARK-1

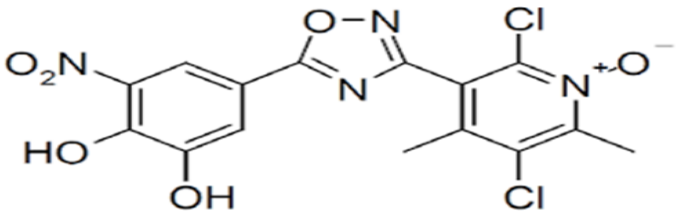
The BIPARK-1 investigators organized a phase III trial that enrolled 600 patients aged 30-83 years from 106 specialist centers across 19 European countries and Russia.[14] Patients were included in this trial if they had PD for at least three years and a history of clinical improvement with levodopa and/or a decarboxylase inhibitor for at least one year. Another inclusion criterion included a Hoehn and Yahr stage of one to three. Further inclusion criteria include symptoms of motor fluctuations for at least four weeks before screening, with a mean total awake time in the off state of at least one and a half hours. Important exclusion criteria included previous use of entacapone, severe or unpredictable periods in the off state, previous surgery or deep brain stimulation for PD, and a dyskinesia disability score greater than three on item 33 (disability) of the Unified Parkinson's Disease Rating Scale (UPDRS). Other exclusion criteria included a history of neuroleptic malignant syndrome or non-traumatic rhabdomyolysis. Patients with clinically significant and unstable psychiatric disorders or cardiovascular disease were also excluded.

The eligible patients were assigned randomly at a 1:1:1:1 ratio using computer analytics. The different treatment regimens were once-daily doses of opicapone of either 5 mg, 25 mg, or 50 mg, matching placebo, or entacapone 200 mg with each levodopa intake; patients were on a stable regimen of three to eight daily doses of levodopa treatment. Both the investigators and patients were blinded to treatment allocation throughout the whole study. The primary endpoint was the change from baseline to the end of study treatment in absolute time in the off state per day. This was calculated by daily paper patient diaries. Key secondary endpoints that were also diary-based were the change from baseline to the end of study treatment in the proportion of patients achieving at least a one hour reduction in absolute time in the off state per day and the change from baseline to the end of study treatment in the proportion of patients achieving at least a one hour increase in absolute total time in the on state. The trial reported compliance with diary entries was 90-100% at all visits for all groups.

The trial used an intention to treat analysis to test for superiority vs placebo but used the per-protocol analysis for non-inferiority vs entacapone. Of the 600 patients enrolled in the study, 98% of patients completed the trial. For the primary outcome, treatment with opicapone 50 mg was superior to placebo (mean difference in change from baseline -60.8 min; 95% CI, -97.2 to -24.4; p=0.0015) and non-inferior to entacapone (-26.2

Table 1 | Select Opicapone Pharmacokinetics[12]

Absorption	
T_{max}[a]	2 hours
Distribution	
Protein Binding	>99%
Metabolism	
Primary	Sulphonation
Other	Glucuronidation, methylation (by COMT[b]), reduction, and glutathione conjugation.
Elimination	
Cl[c]	87 L/hr
Chemical Structure	5-7 hours



[a]Time to maximum plasma concentration; [b]Catechol-O-Methyltransferase

min; 95% CI,-63.8 to 11.4; p=0.0051). Treatment with opicapone 5 mg (-35.2 min; 95% CI, 71.4 to 0.9 ; p=0.056) or 25 mg (-29.9 min; 95% CI, -66.3 to 6.5; p=0.080) was not significantly different from treatment with placebo. For the secondary endpoint of the proportion achieving a one hour reduction of absolute time in the off-state, treatment with opicapone 50 mg (odds ratio 2.5; 95% CI, 1.5 to 4.3; p=0.001) and opicapone 25 mg (1.7; 95% CI, 1.0-2.8;p=0.046) was found to be superior in this secondary endpoint compared to placebo. Opicapone 5 mg (1.6; 95% CI, 1.0-2.7; p=0.065) was not found to be superior to placebo. For the proportion of patients with an increase in time in the on-state of at least one hour, the opicapone 50 mg group was significantly higher (2.2; 95% CI,1.3-3.8; p=0.003) compared to placebo. It was reported that the percentage of patients who discontinued because of adverse effects due to the treatment was low and similar between the treatment groups. The most common adverse events were diarrhea, visual hallucinations, and dyskinesia across all treatment groups including placebo but the prevalence was low. Overall, regarding the adverse events, opicapone was considered safe and well-tolerated by the investigators.

BIPARK-2

BIPARK-2 was similar to BIPARK-1 in that it was a randomized, international, multicenter, double blind, controlled trial ran for approximately 15 weeks.[15] This study included 71 centers across 12 countries across several different continents including Asia and Africa. Patients were included if they were adult men or women between the years of 30-83, if they had a clinical diagnosis of Parkinson's for at least three years, a Hoehn-Yahr stage of 1 to 3, and at least a one-year history of clinical improvement with levodopa and/or decarboxylase inhibitor therapy. All patients again had to have motor fluctuations for at least four weeks before screening, with a mean total awake off-time of at least one and a half hours. Patients also had to keep reliable diaries and make no more than three errors of marking their status in 30-minute intervals per day in the three days before the baseline visit was randomized. Exclusion criteria were the same as BIPARK-1 study.

Eligible patients were randomized using computer analytics in a 1:1:1 ratio. The treatment regimens differed from that of

Table 2 | Select Primary Endpoint Results of BIPARK Series[14,15,18]

Trial	Primary Endpoint	Intervention	Results: Adjusted Treatment Difference (95% CI[a])	P-Value
BIPARK-1[14]	Change from baseline to end of study treatment in absolute time in the off state per day	Opicapone 50 mg/day vs placebo	-60.8 (-97.2 to -24.4)	0.0015
		Opicapone 25 mg/day vs placebo	-29.9(-66.3 to 6.5)	0.080
		Opicapone 5 mg/day vs placebo	-35.2(-71.4 to 0.9)	0.056
		Entacapone 200 mg w/ every levodopa intake vs placebo	-40.3(-76.2 to -4.3)	0.014
		Opicapone 50 mg/day vs entacapone 200 mg	-26.2(-63.8 to 11.4)	0.0051
BIPARK-2[15]	Change from baseline in absolute off time vs placebo based on patent diaries	Opicapone 50 mg/day vs placebo	-54.3 (96.2 to -12.4)	0.008
		Opicapone 25mg/day vs placebo	-37.2 (-80.8 to 6.4)	0.11
Combined Data: BIPARK Extension Study[18]	Change from baseline to end of study treatment in absolute time in the off state per day	Opicapone 50 mg/day vs placebo	-58.1(-84.5 to -31.7)	0.0001
		Opicapone 25 mg/day vs placebo	-35.1(-62.1 to -8.2)	0.0106

[A]95% Confidence Interval

BIPARK-1; opicapone 25 mg per day, opicapone 50 mg day, or matching placebo were the three different regimens in this study. The double-blind assessments occurred at four-week intervals with the whole trial lasting 14-15 weeks. Like the previous trial, the primary endpoint of the change from baseline in absolute off-time was used. Key secondary endpoints were the proportion of patients achieving at least one-hour reduction in absolute off-time and the proportion of patients achieving at least one-hour increase in absolute on-time at the end of the double-blind phase. These endpoints were assessed using the 24-hour patient diaries; patients were instructed to record their status as "off", "on with troublesome dyskinesia", "on with non-troublesome dyskinesia", "on without dyskinesia", or "asleep" for every 30 minute interval during the day for 3 consecutive days before each visit. The double-blind assessments occurred at four-week intervals throughout the 14-15 weeks of the trial.

For the primary outcome analysis, the adjusted treatment difference compared with placebo group was significant for the opicapone 50 mg opicapone group (mean treatment effect [standard deviation or SD], −54.3 [18.9] minutes ; 95% CI, −96.2 to −12.4 minutes; p = 0.008). However, it was not significant for the opicapone 25 mg opicapone group (treatment effect [SD], −37.2 [19.6] minutes; 95% CI, −80.8 to 6.4 minutes; p = 0.11). For the secondary outcome, the proportion of one hour reduction among off-time responders was significantly higher in both the opicapone 25 mg (78 patients [62.4%]; p = 0.04) and 50 mg (97 patients [66.0%]; p= 0.009) opicapone groups. The other outcome that measured the proportion of one-hour increase of on-time responders was also significantly higher in both the 25 mg (79 patients [63.2%]; p = 0.004) and 50 mg (91 patients [61.9%]; p=0.006) opicapone groups. In terms of safety, more than half of patients in each group including placebo (about 68.6%) experienced at least one adverse event that was either mild or moderate in nature. The most common adverse events in the opicapone vs placebo groups were dyskinesia, constipation, and dry mouth. Most (75%) of patients experiencing dyskinesia were already experiencing dyskinesia at baseline.

Long Term Efficacy of Opicapone in Fluctuating Parkinson's Disease Patients

Both the BIPARK-1 and BIPARK-2 each had a one year open-label extension study to assess the maintenance of the treatment effect of opicapone. The data from both studies were combined together as each had similar designs, inclusion/exclusion criteria, and assessment methods.[18] Both open-label extensions had the same primary outcome which was the change from baseline in absolute off time based on patient diaries. The open-label phase began the day after completing the double-blind phase and lasted for 52 weeks. During this open label-phase, all patients began treatment with opicapone 25 mg including patients in the placebo group. A total of 341 patients (53.9%) increased the opicapone dose to 50 mg if required to control wearing off and tolerated during this phase while 12 patients (1.9%) reduced their opicapone dose to 5 mg due to persistent adverse events. In an event of unacceptable dopaminergic adverse events, the levodopa dose was adjusted, then the opicapone dose was titrated down.

Both the 25 mg opicapone and 50 mg opicapone groups significantly reduced absolute daily off time from a baseline of 6.1 to 6.6 hours. For the treatment effect versus placebo during the double-blind phase, the opicapone mean and 95% confidence interval for the 25 mg opicapone group reduction in off-time was −35.1 min; 95% CI,−62.1 to −8.2 min; p = 0.0106 and for the opicapone 50 mg opicapone group it was −58.1 min; 95% CI,−84.5, −31.7 min; p < 0.0001 . The open-label data showed a maintenance of effect for patients treated with opicapone 50 mg of opicapone throughout the year. The group treated with opicapone 25 mg further benefited from an increased titration to 50 mg of opicapone per day during this phase. Patients treated with opicapone 25 and 50 mg during the double-blind phase had respective mean additional reduction in absolute off-time during the open-label phase were -19.4 min and – 8.2 min versus the open-label baseline. Patients previously treated with placebo had an additional mean reduction of -51.1 min versus the open-label baseline. Serious adverse events occurred in 11.3% of the patients in the open-label phase. The percentage of patients that discontinued because of adverse events during this phase was 9.1%.

Adverse Events

The most common adverse reactions observed during the BIPARK-1 and BIPARK-2 studies were constipation, dyskinesia, weight decrease, loss of consciousness, increased levels of creatine kinase and hypotension.[16] The most common adverse event was dyskinesia at an incidence of 20% from the clinical trials. Other infrequent adverse events include constipation at a rate of 5%, hallucinations at a rate of 3%, and insomnia at a rate of 3%.[12] Common adverse events and their incidence rates can be found in **Table 4**.

Dosage and Administration

The recommended dosage for the treatment of PD along when added onto levodopa is opicapone 50 mg administered orally once daily at bedtime.[12] Opicapone was developed to have a bedtime regimen as it will enhance the provider's flexibility in adjusting the dosages of levodopa without any concern for a potential interaction.[19] It is recommended that patients should not eat food for 1 hour before and for at least 1 hour after intake of opicapone.[12] Patients with moderate hepatic impairment will require a decreased dose of opicapone 25 mg orally once daily at bedtime while patients with severe hepatic impairment should avoid use of opicapone. No clinically significant difference in the pharmacokinetics of opicapone were observed in patients with mild or moderate renal impairment relative to those with normal renal function. Patients with severe renal impairment or end stage renal disease (ESRD) have not been studied, therefore patients in these populations should also avoid use of opicapone.

Contraindications and Precautions

The two contraindications of opicapone are concomitant use of non-selective MAO inhibitors and history of pheochromocytoma, paraganglioma, or other catecholamine secreting neoplasms.12 Precautions include monitoring patients for hypotension and educating patients on the risk for syncope/presyncope. It is also important to counsel patients on the potential of developing drowsiness while engaging in activities of daily livings and to potentially consider discontinuing opicapone or adjusting other sedating medications if developed. Patients on opicapone can experience impulse control issues and/or compulsive disorders such as intense urges to spend money or binge eat. It is essential for the provider to ask specific questions to patients and their caregivers about the development of any new or increased gam-

Table 2 | Select Secondary Endpoint Results of BIPARK Series[14,15,18]

Secondary End-point	Trail	Intervention	Results: OR[a] (95% CI[b])	P-Value
Change from the baseline to the end of study treatment in the proportion of patients achieving at least 1-hour reduction in absolute time in the off state	BIPARK-1[14]	Opicapone 50mg/day vs placebo	2.5 (1.5-4.3)	0.001
		Opicapone 25mg/day vs placebo	1.7(1.0-2.8)	0.046
		Opicapone 5 mg/day vs placebo	1.6(1.0-2.7)	0.065
		Entacapone 200mg w/every levodopa intake vs placebo	1.6(0.9-2.6)	0.094
		Opicapone 50 mg/day vs entacapone	1.6(1.0-2.8)	0.003
	BIPARK-2[15]	Opicapone 50 mg/day vs placebo	1.9(1.2-3.1)	0.009
		Opicapone 25 mg/day vs placebo	1.7(1.0-2.8)	0.046
	Combined Data from BIPARK	Opicapone 50 mg/day vs placebo	1.9(1.2-3.1)	0.009
		Opicapone 25 mg/day vs placebo	1.7(1.0-2.8)	0.04
Change from the baseline to the end of study treatment in the proportion of patients achieving at least 1-hour increase in absolute time in the on state	BIPARK-1[14]	Opicapone 50mg/day vs placebo	2.2(1.3-3.8)	0.003
		Opicapone 25mg/day vs placebo	1.6(0.9-2.6)	0.095
		Opicapone 5 mg/day vs placebo	1.4(0.9-2.5)	0.17
		Entacapone 200mg w/every levodopa intake vs placebo	1.6(1.0-2.7)	0.067
		Opicapone 50 mg/day vs entacapone	1.5(0.8-2.4)	0.15
	BIPARK-2[15]	Opicapone 50 mg/day vs placebo	2.0(1.2-3.2)	0.006
		Opicapone 25 mg/day vs placebo	2.1(1.3-4.3)	0.004
	Combined Data from BIPARK	Opicapone 50 mg/day vs placebo	2.0(1.2-3.2)	0.006
		Opicapone 25 mg/day vs placebo	2.1(1.3-3.4)	0.004

[A]Odds Ratio; [b]95% Confidence Interval

bling urges, uncontrolled spending, or other urges while on this medication.

Clinical Implications

The trial design was a major strength of the evidence behind opicapone's approval. Both BIPARK-1 and BIPARK-2 were randomized, double-blind, controlled trials, helping to minimize bias and confounders, with BIPARK-1 utilizing an active comparator from the same class. BIPARK-1 discovered the effects of opicapone were non-inferior to entacapone, further corroborating the investigators' stance that opicapone is a viable option for reducing these "off-time" episodes. Another strength attributed to both studies was a small percentage of patients lost to follow-up. A limitation of these studies is that the controlled trial of BIPARK-1 with an active comparator and BIPARK-2 was only ran for a short time of 15 weeks. However, both studies included a year-long, open-label phase with evidence that opicapone could potentially maintain its therapeutic effect long term. Controlled trials evaluating the efficacy of opicapone compared to entacapone and tolcapone may offer more insight as to how the long-term therapeutic effects of opicapone fare compared to older COMT inhibitors. Another concern was patients with severe or unpredictable off-episodes were excluded from both trials, limiting the inclusivity of the study population. Both BIPARK trials assessed the primary and secondary endpoints utilizing daily paper diary entries recorded by the patient; this aspect highlights a potential respondent bias that could lead to less accurate results as

Table 4 | Adverse Drug Reactions[12]

Event	Incidence
Dyskinesia	20%
Constipation	6%
Hypotension/Syncope	5%
Xerostomia	3%
Insomnia	3%
Hypertension	3%

patient had to keep reliable diaries, assess their own status of symptoms and make no more than three mistakes prior to each visit. Although BIPARK-1 was mainly assessed at centers in Europe, BIPARK-2 expanded its centers by including countries outside of Europe such as South Africa, India, Argentina, Chile, and South Korea, enhancing its applicability.

Opicapone could be a feasible option in the treatment of the motor fluctuations in PD. Previously, entacapone was the most prescribed COMT inhibitor for adjunct therapy, preferred over tolcapone due to its safety profile. BIPARK-1's results for opicapone showed a non-inferiority to entacapone, however superiority trials between opicapone and entacapone would be needed to help clinicians differentiate between these two therapy options. Similarly, conducting more head to head trials of opicapone with not only COMT inhibitors but also MAO inhibitors and dopamine agonists would help to clarify its place as an adjunctive therapy.

Opicapone is dosed once a day which could make it more attractive to the patients than entacapone. However, opicapone might cost more than entacapone. On GoodRX, a 90-count prescription of entacapone has an average cost of around $90-$100 and typically is considered in Tier 4 (non-preferred brand/generic drugs) for common insurance companies.[20] Opicapone is expected to launch in the second half of 2020 due to the COVID-19 pandemic and manufacturing issues. Opicapone is expected to come in lower than the "specialty tier" medicines for Parkinson's, which can cost more than $670 per month. Although US pricing has not been exactly set, Neurocrine's CEO, manufacturer of opicapone, stated a desire to have opicapone as affordable as possible for patients with PD.[21,22] If opicapone ultimately is revealed to be cheaper or of similar price as entacapone, providers may be more inclined to prescribe it over entacapone.

Opicapone appears to have an acceptable safety profile from the data analysis of the phase III trials. Pooled analysis indicated that the incidence of treatment emergent adverse effects was similar across the opicapone (3.5%) and placebo groups (4.3%).[23] No serious adverse drug events related to hepatic toxicity were documented. Incidence of gastrointestinal disorders also remained low at 1.5%. During the open-label treatment, 68.1% of patients experienced at least one adverse event but majority were reported as mild to moderate. While the most common adverse event from the clinical trials was dyskinesia, a high percentage of patients (75%) were already experiencing that before starting the clinical trial. The weekly incidence of dyskinesia was reported to decrease after the first six weeks and by week 6 was only 1%.

Conclusion

Ongentys® (opicapone) shows promising benefit for patients as an adjunctive agent to treat patients with Parkinson's Disease experiencing an increase in the off-state. The current data shows that opicapone can be a safe and effective adjunct for patients still experiencing motor fluctuations on their current regimen of carbidopa/levodopa. More data is warranted to determined opicapone's place in therapy relative to other adjunct agents at this time.

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