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Opicapone: A third generation COMT inhibitor

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ABSTRACT

Objective: To provide a drug review of the newly FDA approved catechol-O-methyl transferase (COMT) inhibitor, opicapone, for the use of end-of-motor motor fluctuation in adults with Parkinson's disease. *Data sources*: A literature search of Pubmed was performed till May 2020 using the following key terms: opicapone, Ongentys, and BIA 9-1067. Review articles, clinical trials, and drug monographs were reviewed. *Study selection and data extraction*: Relevant English-language monographs and studies conducted in humans were considered. *Data synthesis*: Opicapone was FDA approved for the treatment of end-of-motor motor fluctuation in adults with Parkinson's disease in April 2020 based on two published randomized clinical trials that were 14 to 15 weeks in duration called BIPARK I and BIPARK II. Based on the clinical trials, 50 mg of opicapone once daily was shown to be noninferior to entacapone and reduced the mean off time by about 50 min when compared to placebo. Most common treatment-emergent adverse events were dyskinesia, falls, insomnia, and elevated blood creatine phosphokinase levels. *Relevance to patient care and clinical practice*: Opicapone overcomes the limitations associated with other COMT inhibitors since it is dosed once daily, well tolerated, and has not been associated with the risk of hepatic failure. When switching from entacapone to opicapone a reduction in "off" time of −39.3 min was also seen. *Conclusions*: Opicapone is a once daily 3rd generation COMT inhibitor that has the potential to benefit patients with Parkinson's disease who are experiencing end-of-motor fluctuations.

Contents

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1. Introduction and overview of pharmacologic therapies for Parkinson's disease

Parkinson's disease (PD) is the second most common age-related neurodegenerative disorder in the world after Alzheimer's disease. The annual incidence of PD in the US for people greater than 45 years old is 572 per 100,000, with a significantly higher incidence in males (1.5 times greater) compared with females [1–5].Table 1

Since its introduction in the late 1960 s, carbidopa/levodopa has continued to be the gold standard for PD therapy [6]. For patients older than 45 years old, initial treatment with carbidopa/levodopa provides patients with better symptom control and increase their quality of life (QoL) for at least 7 years, compared with dopamine agonists or monoamine oxidase B inhibitors [7]. However, long-term treatment with carbidopa/levodopa can lead to motor fluctuations and carbidopa/levodopa induced dyskinesia. Motor fluctuations are alterations between periods marked by a positive response to carbidopa/levodopa ("on") and periods marked by reappearance of Parkinsonian symptoms ("off"). "Wearing off" near the end of the carbidopa/levodopa dose interval is often the first and most encountered motor fluctuation and linked to the short half-life of oral carbidopa/levodopa (60–90 min) [7].

There are several pharmacologic treatment options for end-of-dose motor fluctuations including catechol-O-methyl transferase (COMT) inhibitors. Carbidopa/levodopa is often metabolized in the periphery by the COMT enzyme and thus inhibitors of COMT increase the half-life of carbidopa/levodopa and enhance central levodopa bioavailability. The benefits of combining carbidopa/levodopa with a COMT inhibitor include reducing "off" time and prolonging "on" time in fluctuating patients while increasing motor scores [8]. Currently, two COMT inhibitors, entacapone and tolcapone, have been approved by the FDA as adjunctive therapy to carbidopa/levodopa to manage the "wearing off" effect and increase "on" time. The two drugs differ in their pharmacokinetic (PK) properties adverse effects: tolcapone inhibits both peripheral and central COMT and thus has a relatively long half-life while entacapone only inhibits the peripheral COMT and has a shorter duration of action (2 h). While both drugs can cause nausea/vomiting, orthostatic hypotension, and confusions, only tolcapone can cause fulminant hepatic failure and thus the FDA addition of a black-box warning to its label [9].

2. Data sources

An English literature search of PubMed database was performed (January 2000 to May 2020) using the following key terms: opicapone, Ongentys, and BIA 9–1067. Prescribing information, phase III & open-label trials, and other randomized controlled trials evaluating the efficacy and safety of opicapone in patients with Parkinson's disease were included. In addition, the websites www.clinicaltrials.gov and https://www.accessdata.fda.gov were reviewed.

3. Chemistry of opicapone

Since June 2016, a third COMT inhibitor namely opicapone has been approved in Europe and subsequently available as Ogentys® for the treatment of end-of-dose motor fluctuations in adult patients whose symptoms are not controllable by carbidopa/levodopa [10]. In February 2017, Neurocrine Biosciences entered into an exclusive licensing agreement with BIAL, the maker of opicapone in Europe,

Table 1
Efficacy of opicapone for Parkinson's Disease [22–24].

NCT	Regimen	Study Type	Study Duration	Primary Endpoint Results
BIPARK I	• Placebo, n = 121 • Opicapone 5 mg, n = 122 • Opicapone 25 mg, n = 119 • Opicapone 50 mg, n = 116 • Entacapone 200 mg with every levodopa intake, n = 122	Phase III	14–15 weeks	*Adjusted least-squares mean change from baseline in absolute time in the off state in the full analysis set (SE, 95% CI)* • Placebo: –56·0 min (13·4; –82·3 to –29·7) • Opicapone 5 mg: –91·3 min (13·5; –117·7 to –64·8) • Opicapone 25 mg: –85·9 min (13·7; –112·8 to –59·1) • Opicapone 50 mg: –116·8 min (14·0; –144·2 to –89·4) • Entacapone 200 mg: –96·3 min (13·4; –122·6 to –70·0)Only opicapone 50 mg was superior to placebo (p = 0·0015) and non-inferior to entacapone (p = 0·0051)
BIPARK II	Double-blind phase: • Placebo, n = 144 • Opicapone 25 mg, n = 129 • Opicapone 50 mg, n = 154 Open-label phase • All patients who completed double-blind phase switched to opicapone, n = 367	Phase III	14–15 weeks, followed by 1-year open label phase	Double-blind phase*Mean change in off time (SD)* • Placebo: –64.5 min (14.4) • Opicapone 25 mg: –101.7 min (14.9) • Opicapone 50 mg: –118.8 min (13.8)*Adjusted least-squares mean change from baseline in absolute time in the off state in the full analysis set (SD; 95% CI, p-value)* • Opicapone 25 mg: –37.2 min (19.6; –80.8 to 6.4, p = 0.11) • Opicapone 50 mg: –54.3 min (18.9; −96.2 to −12.4, p = 0.008) Open-label phase • Adjusted mean change from start to the end of open-label phase in off-time: −18.31 (95%CI, −43.56 to 6.95 min) • Mean (SD) total on time increased by 24.9 (156.4) min • Mean (SD) on-time with troublesome dyskinesia increased by 6.0 (129.1) min
Pooled Analysisof BIPARK I and II	Double-blind phase: • Placebo, n = 265 • Opicapone 25 mg, n = 248 • Opicapone 50 mg, n = 270 Open-label phase • All patients who completed double-blind phase switched to opicapone, n = 662	Phase III	14–15 weeks, followed by 1-year open label phase	Double-blind phase:*Mean change in off time (mins)/ treatment estimate (95% CI, p-value)* • Placebo: –55.5 mins/ NA • Opicapone 25 mg: –92.9 mins/ −35.1 (-62.1 to −8.2, p = 0.0106) • Opicapone 50 mg: –119.9 mins/ −58.1 (-84.5 to −31.7, p < 0.0001) Open-label phase*Mean change in off time (mins)* • Previously placebo: –51.1 mins • Previously opicapone 25 mg: –19.4 mins • Previously opicapone 50 mg: –8.2 mins

CI = confidence interval, NA = not applicable, SD = standard deviation, SE = standard error
Note: Data represented in the table is not all inclusive, refer to clinical trial for comparison to placebo and for all data points. Table to be a summary of main outcomes.

for the development of opicapone in North America. More than two years later, on April 24th 2020, opicapone gained its FDA approval an adjunctive treatment to carbidopa/levodopa in patients with Parkinson's disease experiencing OFF episodes [11].

Opicapone has a pyridine N-oxide residue in its structure that provides high-affinity COMT inhibition and avoidance of cell toxicity. Opicapone does not cross the blood–brain barrier (BBB) and inhibits only peripheral COMT enzymes [12–13].

4. Pharmacodynamics and pharmacokinetics of opicapone

Almeida et al have shown that the half-life and COMT inhibition activity of opicapone are dose dependent. After a single oral administration of various doses (10 mg-1,200 mg) of opicapone to healthy male volunteers, the half-life ranged between 0.8 h (50 mg dose) to 3.2 h (1,200 mg dose). Similarly, the maximum COMT inhibition ranged between 36.1% (10 mg dose) to 100% (200–1,200 mg dose). Surprisingly, at 72-hour post-dose, opicapone still exert COMT inhibitory effect, ranging from 5.9% (10 mg) to 54.6% (800 mg dose). The long-lasting effect of opicapone was hypothesized to be due to the complex's slow dissociation rate. In contrast, previous studies have shown that entacapone and tolcapone have shorter effects of durations (8 and 18 h, respectively) [14–16]. That is the main reason why opicapone can be dosed once daily while both tolcapone and entacapone must be dosed repeatedly to maintain its therapeutic effectiveness. The Cmax or AUC of carbidopa/levodopa was not influenced by coadministration with opicapone. Opicapone can also be administered with a moderate meal without compromising its COMT inhibition [17].

Previous studies done by Rocha et al have shown that there is an increase in opicapone level in patients with moderate liver impairment due to a reduced first-pass effect. Currently, there is no data available about opicapone pharmacokinetics in patients with severe liver disease thus the European/British drug package inserts recommends against the use of opicapone in this patient population [18–19].

A high-fat or high caloric meal can decrease the rate and extent of opicapone absorption as demonstrated by delayed peak plasma levels in patients with a full meal compared to patients under fasting conditions. According to the packet insert, opicapone should be taken at bedtime and patient should abstain from eating food for 1 h before or after administration [17]. Sex, age, and ethnicity do not seem to influence opicapone effect and Falcap et al has shown that there was no significant difference in pharmacokinetics and pharmacodynamics between Japanese and Caucasian populations [20–21].

4.1. Clinical trials

4.1.1. BIPARK I [22]

A phase III clinical trial was conducted by Ferreira et al., in aiming to assess the safety and efficacy of opicapone at various doses when compared to placebo and an active comparator entacapone. As a result, 600 patients with Parkinson's disease and motor fluctuations while on carbidopa/levodopa were randomized to receive placebo (n = 121), entacapone 200 mg with every dose of levodopa (n = 122) or either opicapone 5 mg (n = 122), 25 mg (n = 119), or 50 mg (n = 115) daily. The mean change in the absolute time in the off state was −56 min (SE 13.4; 95% CI −82.3 to −29.7) for placebo, −96.3 min,(13.4; −122.6 to −70) for entacapone, −91.3 min (13.5; −117.7 to −64.8) for opicapone 5 mg, −85.9 min (13.7; −112.8 to −59.1) for opicapone 25 mg, and −116.8 min (14:-144.2 to −89.4) for opicapone50 mg. The study demonstrated that opicapone 50 mg was superior to placebo with a mean difference in change from baseline of −60.8 min, 95% CI −97.2 to −24.4; p = 0.0015. Opicapone 50 mg was also found to be non-inferior to entacapone with a mean difference in change from baseline of −26.2 min, 95% CI −63.8 to11.4; p = 0.0051. Opicapone 5 mg and 25 mg did not show a statistically significant difference from treatment with placebo. The limitations of the study were the exclusion of patients with severe or unpredictable off episodes and/or patients with severe dyskinesia and so the results can only be extrapolated to patients with predictable off periods. However, the study had various strengths as it was designed to determine non-inferiority to an active comparator, was powered to 97% with sample sizes greater than 100 patients per treatment group, and drop-out rates for opicapone 50 mg was comparable to entacapone 200 mg, 7.8% vs 12% respectively.

4.1.2. BIPARK II [23]

In another phase III clinical trial conducted by Lees et al., opicapone 25 mg and 50 mg were compared to placebo to determine the safety and efficacy in treating motor fluctuations for patients with Parkinson's disease. A total of 427 patients were enrolled in the double-blind phase and randomized to receive placebo (n = 144), 25 mg of opicapone (n = 129), or 50 mg of opicapone (n = 154). The double-blind phase of the clinical trial demonstrated that there was a statistically significant difference between opicapone 50 mg and placebo. The adjusted least-squares mean change from baseline in absolute time in the off state in the full analysis set was–54.3 min (18.9; −96.2 to −12.4, p = 0.008) for opicapone 50 mg. The difference between placebo and opicapone 25 mg was not statistically significant. This randomized, placebo controlled, double-blind phase was followed by a 1-year open-label phase in which all patients were initiated on 25 mg of opicapone which could be titrated up to 50 mg if greater symptomatic control was needed. A total of 286 patients completed the 1-year open label phase. The open-label phase showed that the off-time reduction was maintained with an adjusted mean change from start to the end of open-label phase in off-time of −18.31 min (95%CI, −43.56 to 6.95). The limitations of the study were similar to BIPARK I as patients with severe or unpredictable off times were excluded.

4.1.3. Pooled analysis [24]

In 2019, a pooled analysis of the BIPARK I and BIPARK II double-blind phase and 1-year open-label phase was published to assess the efficacy of opicapone 25 mg and 50 mg as adjunct to carbidopa/levodopa when compared to placebo for managing motor fluctuations in patients with Parkinson's disease. In the double-blind phase of the pooled analysis it showed that the treatment effect of opicapone 25 mg (n = 241) and 50 mg (n = 262) were statistically significant compared to placebo (n = 255). When compared to placebo the treatment effect for opicapone 25 mg was −35.1 min (95% CI −62.1 to −8.2, p = 0.0106) and for opicapone 50 mg was −58.1 min (95% CI −84.5 to −31.7, p < 0.0001). Treatment effect was determined by taking the difference between treatment group and placebo of the mean reduction in absolute off time in minutes. A total of 633 patients were pooled for analysis of the open-label phase and the mean reduction in absolute off time for those previously on the placebo group (n = 215) was −51.1 min, those previously on opicapone 25 mg (n = 202) was −19.4 min, and those previously on opicapone 50 mg (n = 216) was −8.2 min. The results showed there was a benefit in reductions of off time from optimizing therapy by switching to opicapone 50 mg.

4.2. Other clinical trials

In May of 2018 the Journal of Neurology published a 52- week open label trial that was an extension of BIPARK I to evaluate the effectiveness of opicapone as add-therapy of levodopa and after switching from entacapone. A total of 495 patients were enrolled in the study and previous treatment during the double-blind phase III trial were as follows: placebo (n = 99), opicapone 5 mg (n = 100), opicapone 25 mg (n = 98), opicapone 50 mg (n = 98), and entacapone

(n = 100). All patients were switched to opicapone 25 mg for 1 week and dose titration was permitted based on tolerability and efficacy. As a result, 42.6% of the patients were on opicapone 50 mg, 5.1% were on opicapone 5 mg, and the rest remained on 25 mg. This study demonstrated that the efficacy of opicapone 50 mg was maintained after 52-weeks and those switched to 50 mg saw a further decrease in "off" time. When compared to the baseline "off" time from BIPARK I patients had more than 2 h (126.9 min) reduction and half-hour (33.8 min) reduction if compared to the baseline at the start of the open-label extension. Opicapone was well tolerated throughout the year with no new safety concerns emerging. The most common reported adverse event was dyskinesia (14.5%), which was managed by adjustment of dopaminergic therapy [25].

5. Dosage & administration

Opicapone is commercially available as a 25 mg hard capsule and its recommended dose is 50 mg to be taken at bedtime at least one hour within administration of carbidopa/levodopa. Dose adjustments are not needed for elderly patients, renal impairment, and mild to moderate hepatic impairment. There is no clinical experience in patients with severe hepatic impairment and so use of opicapone is not recommended for this population [17].

6. Safety

6.1. Adverse effects

In clinical trials of opicapone the most common treatment-emergent adverse event (TEAEs) reported were dyskinesias occurring at a frequency of 17.4% within the BIPARK I and BIPARK II clinical trials and 21.5% within the open label 1-year extension trial [26]. However, the incidence of dyskinesia was reported to decrease over time as carbidopa/levodopa and other dopaminergic medications were adjusted. It was also determined that the incidence of dyskinesia did not affect compliance to opicapone [21,26]. Other common dopaminergic TEAEs reported included hallucinations, insomnia, nausea, and orthostatic hypotension [17]. The dopaminergic adverse events are related to opicapone increasing the bioavailability of carbidopa/levodopa by preventing the peripheral breakdown of levodopa by COMT [17,21,26]. Often it will be necessary to adjust the daily dose of carbidpa/levodopa within the first days to first weeks of initiating opicapone or when discontinuing opicapone in order to avoid these dopaminergic associated adverse events [17]. The most common non-dopaminergic TEAEs reported in clinical trials were constipation, dry mouth, muscle spasms, increased blood creatine phosphokinase (CPK) levels, worsening PD, and increased falls [17,21,26].

Compared to the hepatotoxic COMT inhibitor tolcapone, opicapone has not been associated with an increased risk of fulminant liver injury and clinical trials demonstrated that there were no statistically significant changes in blood hepatic enzymes when compared to placebo. It was also found that unlike entacapone, opicapone, had a lower occurrence of diarrhea and urinary discoloration implicating that it would be better tolerated [26]. In general, opicapone has warnings to monitor for signs of hepatotoxicity and of impulse control disorders. Lastly, since lactose is an excipient it is also advised to avoid the use of opicapone in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption [17].

7. Contraindications

Opicapone is contraindicated in patients with hypersensitivity to opicapone or any component or excipient of the formulation. It is also contraindicated in patients with pheochromocytoma, paraganglioma, and other catecholamine secreting neoplasms, with a history of neuroleptic malignant syndrome and/or non-traumatic rhabdomyolysis. The concomitant use with MAOIs that are not used in the treatment of Parkinson's disease is also contraindicated. Examples of contraindicated MAOIs include phenelzine and tranylcypromine [17].

8. Drug interactions

There is a concern that concomitant use with MAOIs can prevent the metabolism of catecholamines and are therefore contraindicated unless indicated for the treatment of PD. Due to the limited experience of concomitant use with tricyclic antidepressants (TCAs) and noradrenaline reuptake inhibitors it was advised to approach with caution if co-administered.

Opicapone is a weak inhibitor of CYP2C8 and of OATP1B1 and caution should be taken when given concomitantly with substrates [17]. For instance, studies with repaglinide have shown an average increase of 30% in the rate of exposure when co-administered with opicapone.

9. Relevance to patient care and clinical practice

Opicapone joins the market as one of the three COMT inhibitors aimed to manage end of dose motor fluctuations associated with use of carbidopa/levodopa. Opicapone may be favored over entacapone since its pharmacokinetics permits for once daily dosing and has shown to be non-inferior to the efficacy of entacapone. Furthermore, opicapone seems to be well tolerated and is associated with a reduced risk of hepatotoxicity when compared to the COMT inhibitor tolcapone. Opicapone may be preferred in patients who are looking to increase compliance by reducing pill burden. Formulary inclusion for restricted users may be prudent to ensure appropriate dose reduction of carbidopa/levodopa during initiation of opicapone.

10. Conclusion

Opicapone is an efficacious and well tolerated COMT inhibitor that may provide additional reduction of "off" time for patients with Parkinson disease even if switched from entacapone. In addition, the once daily dosing of opicapone simplifies the dosing regimen for Parkinson disease patients with minimal adverse effects. Pricing of opicapone within the U.S. is still pending its release into the market, which was delayed due to the SARS-CoV-2 pandemic.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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