MTRAC
Midlands Therapeutics Review and Advisory Committee

Commissioning Support: Opicapone (*Ongentys®▼*)

Management of Parkinson's disease

Commissioning guidance:

Commissioners may wish to bear the following in mind when considering the commissioning of opicapone:

- It was the opinion of the committee that opicapone would be suitable for prescribing in primary care following initiation in secondary care.
- Opicapone is a once-daily treatment unlike entacapone, which is taken with every levodopa dose. In practice however, patients can be prescribed a combined levodopa/DDCI/entacapone tablet, which reduces the burden of tablets taken. Given that opicapone has to be taken one hour before or after the bedtime levodopa dose, it potentially increases dosing frequency, compared with patients on the fixed-dose combination tablet.
- At current prices (rounded to nearest pound), a year's treatment with opicapone 50 mg daily costs £1,142; generic entacapone (1-2g daily) costs £306 to £712 per year (in addition to £150 to £324 for co-careldopa or co-beneldopa [approximate range based on a number of different formulations]).
- The costs for a year's treatment with a combined levodopa/DDCI/entacapone tablet range from £633 (Sastravi®, Stanek®) to £1,265 (Stalevo®). This assumes 5 doses per day; all dose combinations are the same unit price (MIMS February 2017).
- However, some patients may benefit from the additional option offered by opicapone, especially those in whom entacapone is contraindicated, poorly tolerated or poorly effective.

Strength of the evidence for efficacy: relatively strong

The strength of the evidence for efficacy was considered to be relatively strong in that opicapone was found to be non-inferior to the current standard treatment entacapone in patients with Parkinson's disease and end of dose motor fluctuations. Opicapone 50 mg daily treatment resulted in a placebo-subtracted reduction of approximately 60 minutes in mean OFF time compared with a placebo-subtracted reduction of 40 minutes with entacapone; the difference for the active treatments was statistically significant *vs*. placebo but they were not statistically significant from each other.

Description of technology

Opicapone (Ongentys®▼; Bial Pharma Ltd) is a new catechol-O-methyltransferase (COMT) inhibitor. It is licensed as adjunctive therapy to preparations of levodopa/ DOPA decarboxylase inhibitors (DDCI) in adult patients with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations.

The recommended dose is 50 mg daily, at bedtime, at least one hour before or after levodopa combinations. Opicapone enhances the effects of levodopa. Hence, it is often necessary to adjust levodopa dosage within the first days to first weeks after initiating the treatment with opicapone. For full details of the product, please go to the Summary of Product Characteristics (SPC).

Background

Parkinson's disease (PD) is a progressive neurodegenerative condition characterised by tremor, rigidity (increased resistance during passive joint movement) and bradykinesia (slowed movement).[1] There are also non-motor complications associated with PD that can occur as early symptoms[2]; these are impaired olfaction, constipation, dementia (about 40% of individuals), depression, anxiety, psychosis, sleep disturbance, autonomic disturbances, falls, and pain.[1]

The prevalence of PD is estimated at 0.1 to 0.2% of the general population (5,600 to 11,200 people in the West Midlands). The disease occurs in about 1% of people over 65, rising to 2% in people over 80.[1]

There are currently no disease-modifying therapies available for PD; only symptomatic treatment to aid continuance of normal daily activities. People with mid-to-late stage PD need treatment with levodopa (alone, or in combination with the dopa-decarboxylase inhibitors benserazide or carbidopa). In time, end-of-dose motor fluctuations in symptoms occur with levodopa treatment and require adjunctive therapy with dopamine receptor agonists (pramipexole, ropinirole or rotigotine), apomorphine, MAO-B inhibitors (selegiline, rasagiline or safinamide), or catechol-O-methyl transferase (COMT) inhibitors (entacapone, opicapone, or tolcapone *[risk of hepatoxicity]*).

The draft update of the NICE clinical guideline on the Parkinson's disease in adults: diagnosis and management (2016) advised that if a person with PD has developed dyskinesia and/or motor fluctuations, including medicines 'wearing off', advice should be sought from a healthcare professional with specialist expertise in PD before modifying therapy. In these circumstances, a choice of dopamine agonists, MAO-B inhibitors or COMT inhibitors should be offered as adjuncts to levodopa after discussion with the person about their clinical and lifestyle circumstances, and their preferences, taking into account the potential benefits and harms of the different drug classes. The final version of this guideline is expected in April 2017.

Clinical evidence for efficacy

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Two phase III, randomised, placebo-controlled trials (total n = 1,027) evaluated opicapone as adjunctive therapy to levodopa/DDCI for the treatment of PD. BIPARK-I[3] evaluated opicapone 5mg, 25mg or 50mg daily, and used entacapone (200 mg per levodopa dose) as an active comparator. The second trial (BIPARK-II[4]) evaluated opicapone 25 or 50 mg daily, and included a 12 month open-label extension phase. Both trials included participants aged 30 to 83 years with a diagnosis of PD for at least three years with end-of-dose motor fluctuations, and a Hoehn and Yahr stage 1 to 3 in the ON state. Participants also had to be on a stable optimised regimen of levodopa/ DDCI with clinical improvements for at least 1 year.

The primary outcome measure in both trials was the change from baseline to the end of study treatment in absolute time in the 'OFF' state, assessed by daily patient diaries. Secondary endpoints included the change from baseline to study end in the proportion of patients achieving at least a 1-hour reduction in absolute time in the 'OFF' state (defined as responders), and the change from baseline to the end of study treatment in the proportion of patients achieving at least a 1-hour increase in absolute total time in the 'ON' state. Quality of life scales included the Unified Parkinson's disease rating scale (UPDRS), the Parkinson's Disease Sleep Scale (PDSS), the 39-item Parkinson's Disease Questionnaire (PDQ-39), Non-Motor Symptoms Scale (NMSS), and the Clinician's and Patient's Global Impression of Change (CGI-C and PGI-C).

Results

Absolute time in the OFF state: In both trials, only the opicapone 50 mg daily dose was shown to give a significantly greater improvement (reduction) in time in the OFF state than with placebo (~2hrs *vs*. ~1 hr). In BIPARK-I, opicapone 50 mg was also shown to be non-inferior to entacapone for this outcome (p = 0.0051).[3,4] In this trial, the mean change from baseline in OFF time was a reduction of 117 minutes and 96 minutes for opicapone 50 mg and entacapone, respectively, *vs*. 56 minutes with placebo.[3]

Secondary outcomes: In the BIPARK-I trial, the proportion of participants 'responding to treatment' and showing a reduction in OFF time of at least one hour was significantly greater for the opicapone 25 and 50 mg groups than for placebo. The proportion of participants showing an increase in ON time of at least one hour was also significantly greater with the 50 mg opicapone dose compared with placebo. No significant differences were noted in these outcomes for entacapone *versus* placebo, and there was no significant difference for opicapone *versus* entacapone.[3]

In the BIPARK-II trial, similar data were reported for the comparisons of opicapone 25 mg or 50 mg *versus* placebo, and both doses were shown to be significantly better than placebo for OFF and ON time responders.[4]

Patients' global assessment of change (PGI-C): In the BIPARK-I trial, more opicapone-treated patients than those receiving placebo reported minimal, much, or very much greater improvement from baseline for all doses evaluated; 5 mg (64.7% of participants reported improvement; p = 0.012), 25 mg (63.7%; p = 0.005) and 50 mg (72.1%; p = 0.0008).[3]

In the BIPARK-II trial, there was no significant difference between the opicapone treatment groups and placebo for the overall outcome. A higher proportion of opicapone-treated participants reported that they were 'much' or 'very much' improved (29.8% and 25.3% for the 25 mg and 50 mg dose groups, respectively) compared with 20.1% of placebo-treated participants.[4,5]

Clinicians' global assessment of change (CGI-C): In the BIPARK-I trial, treatment with opicapone 25 mg (60.3%; p = 0.03) and 50 mg (73%;p = 0.0005) doses showed significantly greater improvements *versus* placebo.[3]

No differences were noted for entacapone compared with placebo in either of these assessments of improvement. Additionally, more participants in the opicapone 50 mg group than in the entacapone group had improved on the CGI-C (p=0·0070), and the 25 mg and 50 mg doses, respectively, were significantly more improved than entacapone according to the PGI-C (p = 0.037 and p = 0·0091 for 25 and 50 mg doses).

In the BIPARK-II trial, no significant differences were reported for opicapone *versus* placebo for the overall outcome score. More opicapone-treated participants were assessed as 'much' or 'very much' improved (27.4% and 23.2% for the 25 mg and 50 mg dose groups, respectively), compared with placebo-treated participants (18.6%).[4,5]

Quality of life: In both trials, all groups showed numerical improvements from baseline in UPDRS, PDSS, NMSS, and PDQ-39 scores, but the differences between active treatment and placebo groups were not significant.[3,4]

Adverse events

A total of 792 people were treated with opicapone during the clinical trial development programme. In the phase 3 trials, dyskinesia was the most frequently reported treatment-emergent adverse event (TEAE) in all treatment groups. There was a higher incidence of dyskinesia in the opicapone treatment groups compared with placebo and a slightly higher incidence *versus* entacapone. Other related TEAEs reported more frequently in the opicapone groups compared with placebo included insomnia, constipation, increased blood creatinine phosphokinase, dizziness and dry mouth. Hallucinations and impulse control disorders are also described in the SPC.

References

1. Parkinson's disease. NICE CKS 2016
2. Kalia LV, Lang AE. Parkinson's disease. *Lancet* 2015; 386(9996):896-912.
3. Ferreira JJ et al. *Lancet Neurol* 2015.
4. Lees AJ et al. *JAMA Neurol* 2016.
5. Assessment report: Ongentys. European Medicines Agency 2016

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