NHS Bedfordshire Clinical Commissioning Group

NHS Luton Clinical Commissioning Group

Bedfordshire and Luton Joint Prescribing Committee

December 2017
Review Date: December 2020

Bulletin 262: Opicapone for Parkinson's Disease

JPC Recommendations:

- The use of opicapone is supported as an adjunctive treatment to levodopa/dopa-decarboxylase inhibitor therapy in adults with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations.
- It should be used as a second line agent for those patients who do not respond to or tolerate entacapone.
- Opicapone treatment must be initiated by a Neurologist who specialises in Parkinson's Disease and may be continued by the GP.
- An audit of patient outcomes should be presented to the JPC in 12 months time.

New Medicine Review –Opicapone

Medicine	Opicapone (Ongentys) 50mg capsules
Document status	Final
Date of last revision	N/A
Proposed Sector of prescribing	Specialist initiation by a Neurologist and continuation in primary care when the patient is stable.
Introduction **Summary Key points** **Evidence level**	Oral opicapone, a potent, third-generation, long-acting, peripheral catechol-O-methyltransferase (COMT) inhibitor, is indicated as adjunctive treatment to levodopa/dopa-decarboxylase inhibitor therapy in adults with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations. The main clinical benefits of opicapone 50mg daily up to 15 weeks were reduced off-time of 60.8 minutes and an increase in on-time without troublesome dyskinesia of 62.6 minutes, compared with placebo. The effect was maintained at 1 year in an open-label extension study. Opicapone 50mg was shown to be non-inferior to entacapone 200mg for reducing off-time. Opicapone has the advantage of once daily administration, but there is no evidence of significant additional benefit compared to entacapone. Overall, opicapone was well tolerated with a relatively low incidence of adverse effects compared with placebo and entacapone. Dyskinesia was the most commonly reported adverse event. Its intended use is for initiation by a Neurologist who specialises in Parkinson's: • As a safe and effective second line COMT inhibitor, for those patients with end of dose motor fluctuations/OFF periods who do not respond to or tolerate entacapone. The current second line COMT inhibitor, tolcapone, requires blood monitoring because of rare but potentially serious hepatotoxicity. • Patients with severe motor fluctuations, with significant daily OFF time and end of dose fluctuations, in who all other drug combinations have failed, and the only remaining options are invasive advanced therapies (deep brain stimulation, apomorphine, or levodopa-carbidopa intestinal gel). Opicapone is significantly more expensive than generic entacapone, but may be preferable to tolcapone in patients who have discontinued entacapone due to potential tolcapone-induced hepatotoxicity and the need for monitoring. Tolcapone is only indicated if other COMT-inhibitors cannot be used. The cost of opicapone is comparable to the lower dose of tolcapone (higher dose rarely used). Potential cost to the CCGs: as opicapone is placed as second-line to generic entacapone, the costs should be neutral or slightly better as no monitoring is required for hepatotoxicity. It is of course considerably more cost-effective than other alternatives in the pathway. A pathway for use the use of opicapone is also included - **see appendix 1**

The intervention Mechanism of action	Opicapone is a peripheral, selective and reversible inhibitor of catechol-O-methyl transferase (COMT) that increases levodopa plasma levels when used in combination with levodopa and a peripheral DOPA decarboxylase inhibitor (DDCI), such as carbidopa or benserazide.
Licensed indication	Opicapone is indicated 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.[1]
Formulation/Available Products	50mg hard capsule.[1]
Usual dosage	50mg once-daily at bedtime at least one hour before or after levodopa combinations.[1]
Treatment alternatives/ place in therapy	Other COMT-inhibitors: entacapone or tolcapone. Its intended use is for initiation by a Neurologist who specialises in Parkinson's: • As a safe and effective second line COMT inhibitor, for those patients with end of dose motor fluctuations/OFF periods who do not respond to or tolerate entacapone. The current second line COMT inhibitor, tolcapone, requires blood monitoring because of rare but potentially serious hepatotoxicity. • Patients with severe motor fluctuations, with significant daily OFF time and end of dose fluctuations, in who all other drug combinations have failed, and the only remaining options are invasive advanced therapies (deep brain stimulation, apomorphine, or levodopa-carbidopa intestinal gel).
Future alternatives	
National guidance	**NICE Guideline NG71: Parkinson's Disease in Adults** Adjuvant treatment of motor symptoms should be on the recommendation of a Parkinson's specialist. Choice includes dopamine agonists, MAO-B-inhibitors or catechol-O-methyl-transferase (COMT)-inhibitors as adjuncts to levodopa therapy. The guidelines make no distinction on choice within these groups but there is a separate NICE Evidence Summary for opicapone.[2]
Local Guidance	**Follow NICE Guidelines.**
Evidence for use	The efficacy of opicapone has been evaluated in two randomised, controlled, double-blind, multinational phase 3 studies (BIPARK-I and BIPARK-II) of 14 to 15 weeks duration, followed by an open-label extension of up to one-year.[3,4] Both studies included patients aged 30–83 years with idiopathic PD for ≥3 years, a modified Hoehn and Yahr stage of I-III (during the on state), had received L-Dopa/DDCI for ≥1 year with clear clinical improvement and were on stable optimised dosages of L-Dopa/DDCI (3 – 8 daily doses) and other PD drugs for ≥4 weeks before screening. Patients had to have signs of EoD motor fluctuations for ≥4 weeks before screening, with average total daily OFF-time while awake of ≥1.5 hours, excluding morning akinesia.[3,4] In BIPARK-I, a total of 600 patients were randomised to oral opicapone (5 mg, 25 mg or 50 mg once daily), placebo or entacapone 200 mg (active comparator).2 In BIPARK-II, a total of 427 patients were randomised to opicapone (25 mg or 50 mg) or placebo.3 The primary outcome for both studies was the mean change from baseline in absolute OFF-time, as assessed by unified Parkinson's disease rating scale (UPDRS) scores using daily patient diaries. Key secondary outcomes were OFF-time responders (≥1 hour reduction in absolute OFF-time from baseline), and

ON-time responders (≥1 hour increase in absolute ON-time from baseline). The discussion here focuses on the recommended dosage of opicapone, 50 mg once daily. In both studies, adjunctive opicapone 50mg/day significantly reduced the time spent in the OFF state (primary endpoint) compared to placebo (table 1). The proportions of OFF-time and ON-time responders were also significantly higher in the opicapone 50mg/day group compared to placebo in both studies. Opicapone 50mg/day was associated with greater improvements in both patient and Clinicians and Patient's Global Impression of Change than placebo, but the differences were only statistically significant in the BIPARK-I study. No statistically significant differences were observed between opicapone and placebo in health-related quality of life, motor scores or daily activity scores in either trial.[3-5]

In BIPARK-I, opicapone 50 mg was shown to be non-inferior to entacapone with a mean between-group difference of -26.2 min; 95 % CI -63.8 to 11.4; p=0.0051.2 However, the study was not designed or powered to evaluate the superiority of opicapone vs. entacapone. An integrated analysis of the BIPARK trials performed by the EMA confirmed the results of the individual trials demonstrating superiority of the 50 mg dose over placebo in reducing the time spent in the OFF state (difference-64.4 minutes, p<0.0001).[5]

In the open-label (OL) extension studies of BIPARK-I and II (n = 862), the efficacy of opicapone achieved during the initial 14 to 15 week double-blind (DB) treatment Phase appeared to be maintained over the course of a subsequent year of treatment.[4,5] In BIPARK-II, OFF-time decreased by a further 21.8 minutes relative to the OL baseline, (-126.3 minutes relative to original DB baseline). Similarly, total ON-time had increased by 24.9 minutes from OL baseline (127.3 minutes vs. DB baseline).3,4 A draft report of the BIPARK-I OL extension study showed generally similar results.[6]

Table 1. Efficacy of opicapone in the phase 3 BIPARK-I and BIPARK-II trials – LOCF (FAS).[3-5]

Study, treatment (no. of pts)	Change in absolute OFF-time in mins	Difference vs. placebo in absolute OFF-time (95% CI)	OFF-state responder rate (OR; 95% CI)	ON-state responder rate (OR; 95% CI)
BIPARK I				
OPI 5 mg (119)	-91.3	-35.2 (-71.4 to 0.9)	60% (1.6; 1.0-2.7)	55% (1.4; 0.9-2.4)
OPI 25 mg (116)	-85.9	-29.9 (-66.6 to 6.5)	60% (1.7; 1.0-2.8) p=0.04	57% (1.6; 0.9-2.6)
OPI 50 mg (115)	-116.8	-60.8 (-97.2 to -24.4) p=0.001	70% (2.5; 1.5-4.3) p=0.001	65% (2.2; 1.3-3.8) p=0.003
ENT 200 mg (120)	-96.3	-40.3 (-76.2 to -4.3) p=0.01	58% (1.6; 0.9-2.6	58% (1.6; 1.0-2.7)
Placebo (120)	-56.0	-	48%	46%
BIPARK II				
OPI 25 mg (125)	-101.7	-37.2 (-80.8 to 6.4)	62% (1.7; 1.0-2.8) p=0.04	63% (2.1; 1.3-3.4) p=0.004
OPI 50 mg (147)	-118.8	-54.3 (-96.2 to -12.4) p=0.008	66% (1.9; 1.2-3.1) p=0.009	62% (2.0; 1.2-3.2) p=0.006
Placebo (135)	-64.5	-	50%	45%

LOCF = last post-baseline observation carried forward, FAS = full analysis set.

Safety*

Adjunctive opicapone was generally well tolerated and the majority of adverse events were comparable to those observed with other COMT-inhibitors.[2-5] The most common adverse reactions reported were nervous system disorders. Dyskinesia was the most frequently reported treatment-emergent adverse reaction (17.7%). Other common adverse reactions include dizziness, somnolence and headache. For the full list of all side effects reported with opicapone, see the SPC.[1]

Opicapone must not be used in:

- patients with tumours of the adrenal glands such as pheochromocytoma and paraganglioma;
- patients with a history of neuroleptic malignant syndrome or rhabdomyolysis ;
- patients taking non-selective monoamine oxidase (MAO) inhibitors except when used to treat Parkinson's disease.

Patients should be monitored regularly for the development of impulse control disorders and review of treatment is recommended if such symptoms develop.[1]

Costs
Tariff status
Activity costs

Drug & Dosage	30 day cost/per patient	Annual Cost per patient
Opicapone 50mg OD	£93.90	£1126.80
Tolcapone 100mg TDS	£95.20	£1142.40
Tolcapone 200mg TDS	£190.40	£2284.80
Generic entacapone 200 mg taken with each levodopa/DDCI dose up to 10 times a day[1]	QDS £14.24 7xOD £24.92	£170.88 to £299

Prices from current on-line MIMS.

N.B. Doses are for general comparison and do not imply therapeutic equivalence

1. Specialists who commented on the NICE evidence summary suggested that for most people, entacapone is taken between 4 and 7 times a day.

Cost effectiveness (if available)

No cost-effectiveness studies found.

Potential number of patients in Bedfordshire and Luton
Impact per 100,000 population

Affordability considerations

Estimated number of patients is 50 across the County. This is based on the assumption that 25% would be treated with entacapone and that an estimated 20% of entacapone users will be poorly controlled or intolerant of entacapone so may be suitable for switching to opicapone.

PD is a common, progressive neurodegenerative condition, estimated to affect up to 160 people per 100,000 of the UK population, with an annual incidence of 15–20 per 100,000.

At a cost of £93.90 for a pack of 30 x 50 mg capsules, opicapone is significantly more expensive than generic entacapone (see cost charts). It is, however, comparable to tolcapone without the need for close monitoring. It is also considerably less expensive than other options such as:

Duodopa intestinal gel: typical daily cassette cost of £77; annual costs £28,105.

	Deep brain stimulation costs: initial surgery £35,000 plus £10,000 for battery changes every 5 years and ongoing specialist nursing costs. The prevalence of PD is likely to increase substantially in the near future due to an ageing population. The majority of direct NHS costs are generally associated with hospital care, specialist nursing and therapy services, with the costs for drug treatments relatively low in comparison. Any drug treatments that potentially delay the progression of the disease or reduce the debilitating symptoms could have a significant impact on total costs.
Decisions from other bodies **Comments sought from –**	SMC: opicapone not currently recommended as the company has not made a submission. This indication is, however, currently under review.
Evidence strengths and limitations	The strength of the evidence for efficacy is considered to be relatively strong, in that opicapone was found to be non-inferior to the current standard treatment entacapone in two well-designed randomised controlled trials. The open-label extensions studies may be considered as indicative of maintenance of effect, but due to the potential for selection bias, the results of such open-label extension studies should be treated with caution. Baseline absolute OFF-time ranged from 6.1 hours to 6.9 hours in both studies, which may suggest that subjects may have been receiving suboptimal doses of L-dopa therapy. The studies excluded a broad range of PD patients such as those with severe and/or unpredictable OFF periods, and those with severe dyskinesia. However, the studies were designed to investigate the efficacy of opicapone in patients with end-of-dose wearing off, which is generally characterised by predictability of OFF episodes.[8]

PAC New Drug Template – Adapted from East Anglia Medicines Information, NHS Suffolk, NHS Cambridgeshire and NHS Derby templates

**Consult Summary of Prescribing Characteristics for full prescribing detail.*

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

Appendix 1

Management of the Motor Symptoms of Parkinson's disease

EARLY DISEASE
(Typically 0-5 years after diagnosis)
(when symptomatic therapy required)

Levodopa/ dopa decarboxylase inhibitor (LD): **Sinemet®/Madopar®**
Dopamine agonist (DA): **Ropinirole/Pramipexole/Rotigotine patch**
Monoamine Oxidase B (MAO-B) inhibitor: **Selegiline/ Rasagiline**
There is no universal first-choice drug therapy for people with early PD. The specialist will take a number of factors into account including, age of onset, severity of motor symptoms, neuropsychiatric and cognitive impairments, preferred mode and frequency of administration, lifestyle characteristics, patient preference

MOTOR FLUCTUATIONS
(Typically 5-10 years after diagnosis)
Patient often have combinations of any of the following:

Inadequate symptomatic response
Consider adjunct dopaminergic therapy (LD/DA/MAO-B)

End (start) of dose motor fluctuations
Diphasic dyskinesias
Optimise timings of LD therapy
Optimise LD/DA/MAO-B regime
COMT inhibitor (Entacapone/Sastravi®)
COMT inhibitor (Tolcapone/Opicapone
If Entacapone not tolerated or ineffective)

Unpredictable OFF/ dose failure
Madopar® dispersible
Consider COMT inhibitor
Entacapone
Tolcapone/ Opicapone if entacapone not tolerated or ineffective

Disabling peak dose dyskinesias
Optimise DA/LD/MAO-B
Fractionate or lower LD

Amantadine

Refractory tremor
Optimise DA/LD/MAO-B

* *

REFRACTORY MOTOR COMPLICATIONS
(typically 10 years+)

- excessive daily OFF
- troublesome dyskinesias
- refractory tremor
- all other non-invasive/oral medication

Combinations unsuccessful

Intermittent apomorphine injections
Continuous apomorphine infusion

Deep brain stimulation (STN, Gpi, VIM)

Levodopa – carbidopa intestinal gel

* Opicapone would be used in patients with motor fluctuations and significant OFF time, in whom existing oral strategies have failed in order to delay or prevent progression to invasive surgical or infusion therapies, as indicated on the pathway

Appendix 2 - Search Strategy

NICE, SMC, Specialist Pharmacy Services, Embase search.

List of references

1. Bial Pharma. Summary of Product Characteristics. Ongentys 50 mg hard capsules. Last Updated on eMC 21- Sep-2016. Available at: http://www.medicines.org.uk/emc/medicine/32365
2. NICE Guideline NG71: Parkinson's Disease in Adults, July 2017.
3. Ferreira JJ et al. Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomised, double-blind, controlled trial. Lancet Neurol 2015.
4. Lees AJ et al. Opicapone as Adjunct to Levodopa Therapy in Patients With Parkinson Disease and Motor Fluctuations: A Randomized Clinical Trial. JAMA Neurol 2016.
5. EMA - (CHMP). Ongentys – Opicapone. European Public Assessment Report (EPAR). EMEA/H/C/002790/0000. 18 April 2016 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/ human/002790/WC500209538.pdf.
6. Ferreira, JJ et al. Safety and tolerability of opicapone in the treatment of Parkinson's disease and motor fluctuations: Analysis of pooled phase III studies [abstract]. Movement Disorders 2015;30 Suppl 1 :220.
7. NICE Evidence Summary (ES9). March 2017. Parkinson's disease with end-of-dose-fluctuations: opicapone.
8. Regional Drug & Therapeutics Centre, Newcastle-upon-Tyne as part of UKMi network (NICE accredited). New drug Evaluation: Opicapone for mid to late stage Parkinson's disease. Number 151, April 2017.

Bedfordshire and Luton Joint Prescribing Committee (JPC)
Assessment against Ethical and Commissioning Principles

Treatment assessed (December 2017):
Opicapone for Parkinson's Disease

JPC Recommendations:

- The use of opicapone is supported as an adjunctive treatment to levodopa/dopa-decarboxylase inhibitor therapy in adults with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations.
- It should be used as a second line agent for those patients who do not respond to or tolerate entacapone.
- Opicapone treatment must be initiated by a Neurologist who specialises in Parkinson's Disease and may be continued by the GP.
- An audit of patient outcomes should be presented to the JPC in 12 months time.

1) Clinical Effectiveness

The main clinical benefits of opicapone 50mg daily up to 15 weeks were reduced off-time of 60.8 minutes and an increase in on-time without troublesome dyskinesia of 62.6 minutes, compared with placebo. The effect was maintained at 1 year in an open-label extension study. Opicapone 50mg was shown to be non-inferior to entacapone 200mg for reducing off-time. Opicapone has the advantage of once daily administration, but there is no evidence of significant additional benefit compared to entacapone.

2) Cost Effectiveness

For second-line use after generic entacapone, this intervention is cost-neutral as the costs are the same as tolcapone (at the lower dose range) but without the need for monitoring of liver function.

3) Equity

No impact envisaged.

4) Needs of the community

Offers a safer alternative to tolcapone.

5) Need for healthcare (incorporates patient choice and exceptional need)

As 20% of entacapone users will become intolerant or poorly controlled, opicapone offers a safer alternative second-line COMT-inhibitor than tolcapone. Tolcapone is only licensed to be used where other COMT-inhibitors are unsuitable.

6) Policy drivers

Patient safety. Tolcapone-induced hepatotoxicity whilst rare can be potentially fatal and requires monitoring. So far, opicapone seems to be better tolerated than tolcapone with no relevant liver function abnormalities occurring in clinical trials.

7) Disinvestment

It is envisaged that opicapone will replace tolcapone unless new adverse reactions are revealed in post-marketing studies.

The JPC agreed the following sections within the CCG Ethical and Commissioning Framework were not relevant to JPC discussions: Health Outcomes, Access, and Affordability.

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*