

Parkinson's disease with end-of-dose motor fluctuations: opicapone

Evidence summary

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[nice.org.uk/guidance/es9](https://www.nice.org.uk/guidance/es9)

Key points

The content of this evidence summary was up-to-date in March 2017. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#), or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Regulatory status: New medicine. Opicapone is a catechol-O-methyl transferase (COMT) inhibitor. It received a [European marketing authorisation](#) in June 2016 and was launched in the UK in October 2016. It is licensed for adjuvant therapy to preparations of levodopa/DOPA decarboxylase inhibitor (DDCI) in adults with Parkinson's disease who are experiencing end-of-dose motor fluctuations and cannot be stabilised on those combinations.

Overview

This evidence summary reviewed 1 randomised placebo- and active-controlled trial in people with Parkinson's disease of at least 3-year duration, who were taking a stable dose of levodopa and experiencing end-of-dose motor fluctuations. Most participants were also taking other Parkinson's disease medicines, most commonly a dopamine agonist. There are limited data on the use of opicapone as a first choice adjunct therapy to levodopa.

The main clinical benefits of opicapone 50 mg 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 50 mg was shown to be non-inferior to entacapone 200 mg for reducing off time.

Overall, opicapone was well tolerated with a relatively low incidence of adverse events compared with placebo and entacapone. Dyskinesia was the most commonly reported adverse event. Dose adjustment of levodopa therapy within the first days to first weeks after initiating treatment with opicapone will often be necessary. Specialists who commented on this evidence summary suggested that opicapone may be an option to consider when entacapone is not tolerated or is inadequate at controlling symptoms.

The NICE guideline on [Parkinson's disease](#) makes recommendations on the place in therapy of adjuvant treatments. The choice of treatment will depend on the person's clinical and lifestyle characteristics, and their preferences, after an informed discussion about the benefits and risks of treatment.

A summary to inform local decision-making is shown in table 1.

Table 1 Summary of the evidence on effectiveness, safety, patient factors and resource implications

<p>Effectiveness</p> <ul style="list-style-type: none">• Ferreira et al. 2016 (n=600) found that opicapone, as an adjunct to levodopa, was more effective than placebo at reducing off time in people with Parkinson's disease (mean difference of 60.8 minutes). Improvements in on time without troublesome dyskinesia were also seen in people treated with opicapone (mean difference of 62.6 minutes compared with placebo).• Opicapone was shown to be non-inferior to entacapone for reducing off time.• There was a statistically significant improvement in clinician global impression of change (measured by CGI-C and PGI-C) with opicapone 50 mg compared with placebo.
<p>Safety</p> <ul style="list-style-type: none">• The SPC states that the most common adverse reactions reported were central nervous system disorders with dyskinesia being reported as very common (10 in 100 people or more).• Common (1 in 100 or more) adverse reactions included dizziness, headache and somnolence.

Patient factors

- Opicapone enhances the effects of levodopa. The SPC states it is often necessary to adjust the daily dose of levodopa within the first days to first weeks after starting treatment with opicapone, to reduce levodopa-related dopaminergic adverse reactions such as dyskinesia.
- Opicapone is taken once a day, which may enable a simplified regimen when taken with levodopa compared to other COMT inhibitors.
- Impulse control disorders may occur with dopaminergic medicines and patients and carers should be made aware of the behavioural symptoms of these.
- People taking opicapone should be advised that opicapone in association with levodopa may have major influence on the ability to drive and use machines, due to dizziness, symptomatic orthostatism or somnolence.

Resource implications

- Opicapone 50 mg tablets cost £93.90 for 30 tablets ([MIMS](#), February 2017, excluding VAT).
- 30-day treatment costs (excluding VAT) for: opicapone 50 mg is £93.90 ([MIMS](#), February 2017); entacapone based on maximum dose is £50.30 ([Drug Tariff](#), February 2017); and tolcapone based on 100 mg dose is £85.68 ([MIMS](#), February 2017).

Introduction and current guidance

A NICE guideline on [Parkinson's disease](#) was published in June 2006. An [update](#) of this guideline is in progress and publication is expected in April 2017. The guideline describes Parkinson's disease as a progressive neurodegenerative condition resulting from the death of dopamine-containing cells of the substantia nigra region of the brain.

As Parkinson's disease progresses, most people will develop motor complications and will eventually need levodopa therapy. During the course of the disease motor fluctuations and dyskinesias occur, which may be related to long-term levodopa use or disease progression, or both. Adjuvant treatments may also be needed for people who are not adequately controlled on levodopa alone, with the aim of reducing motor complications and improving quality of life. These include dopamine agonists, monoamine oxidase-B (MAO-B) inhibitors and catechol-O-methyl transferase (COMT) inhibitors.

The NICE guideline states that it is not possible to identify a universal first-choice adjuvant treatment for people with later Parkinson's disease. The choice of adjuvant medicine first prescribed should take into account:

- clinical and lifestyle characteristics
- patient preference, after the patient has been informed of the short- and long-term benefits and drawbacks of the classes of medicines.

It recommends that COMT inhibitors may be used to reduce motor fluctuations in people with later Parkinson's disease.

Product overview

Mode 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 ([summary of product characteristics](#) [SPC]: opicapone and [European public assessment report](#) [EPAR]: opicapone).

Regulatory status

Opicapone ([Ongentys](#), Bial Pharma Limited) is a new medicine that received a European marketing authorisation in June 2016 and was launched in the UK in October 2016. It is licensed for adjuvant therapy for the treatment of Parkinson's disease in adults who are experiencing end-of-dose motor fluctuations and cannot be stabilised on levodopa/DDCI (SPC: opicapone).

Dosing information

The recommended dose of opicapone is 50 mg taken once daily at bedtime at least 1 hour before or after levodopa combinations (SPC: opicapone). The SPC states that dose adjustment to levodopa therapy within the first days to first weeks after initiating treatment with opicapone is often necessary.

No dose adjustment is needed in people with renal impairment or mild hepatic impairment, or in people aged 85 years or less.

Cost

Opicapone 50 mg tablets cost £93.90 for 30 tablets ([MIMS](#), February 2017, excluding VAT).

Evidence review

A literature search was conducted which identified 7 references (see the [search strategy](#) for full details). These references were screened using their titles and abstracts and 1 reference was obtained and assessed for relevance.

From the search, 1 randomised controlled trial (RCT; [Ferreira et al. 2016](#); BIPARK I) was identified and included in the evidence summary. A summary of the included study is shown in table 2 (see the [evidence table](#) for full details).

An additional 14- to 15-week RCT ([Lees et al. 2016](#); BIPARK II) that was considered by the European Medicines Agency during the regulatory process was published after the search was conducted. The results of this study are briefly summarised in the review of the [clinical effectiveness](#).

Table 2 Summary of the included study

Study	Population	Intervention and comparison	Primary outcome
Ferreira et al. 2016 (BIPARK I) RCT	Aged 30 to 83 years with PD and end-of-dose motor fluctuations n=600	Opicapone 5 mg, 25 mg and 50 mg vs placebo or entacapone 200 mg (taken with each levodopa intake)	Mean change in absolute off time from baseline to study end
Abbreviations: PD, Parkinson's disease; RCT, randomised controlled trial.			

Clinical effectiveness

This evidence summary is based on a 14- to 15-week, [double-blind](#), placebo- and active-controlled RCT of opicapone as an adjunct to levodopa in people with Parkinson's disease experiencing end-of-dose motor fluctuations (Ferreira J et al. 2016; BIPARK I). All participants had a clinical diagnosis of Parkinson's disease for 3 or more years and were taking a stable dose of levodopa (immediate- and controlled-release). Many participants were also taking other Parkinson's disease medicines, most commonly a dopamine agonist.

The BIPARK I study evaluated the superiority of opicapone to placebo and also the non-inferiority of opicapone to entacapone 200 mg. There were 5 treatment arms in the study. See table 2 for details.

This evidence summary will mainly focus on reporting the results of the licensed opicapone 50 mg formulation.

Motor symptoms (off and on state)

The primary outcome was the change from baseline to study end in the absolute time in the off state as assessed by using daily participant diaries. Analysis of the outcome used a hierarchical procedure for each opicapone dose, with superiority over placebo being established before determining non-inferiority to entacapone.

At 14 to 15 weeks the mean change from baseline in absolute time in the off state to study end was largest in the opicapone 50 mg group (-116.8 minutes), followed by entacapone (-96.3 minutes) and the placebo group (-56.0 minutes) in the intention to treat [ITT] analysis. The mean difference in change from baseline between opicapone 50 mg and placebo was -60.8 minutes (95% confidence interval [CI] -97.2 to -24.2, $p=0.0015$) demonstrating superiority to placebo (Ferreira et al. 2016). Superiority to placebo was not shown by opicapone 5 mg and 25 mg. There was a statistically significant reduction in the absolute mean off time when entacapone was compared with placebo of -40.3 minutes (95% CI -76.2 to -4.2, $p=0.014$). Ferreira et al. (2016) reported that similar results were seen in the per-protocol analysis (data not shown by the authors).

In the non-inferiority analysis, the mean difference in the absolute time in the off state with opicapone 50 mg compared with entacapone was -26.2 minutes (95% CI -63.8 to 11.4, $p=0.0051$ [per-protocol analysis]). Based on the predefined non-inferiority margin of 30 minutes, opicapone 50 mg was found to be non-inferior to entacapone.

Responder rates for the off and on state (percentage of participants achieving a 1 hour or more reduction in absolute time in the off state or 1 hour or more increase in the absolute time in the on state) were reported by the authors as key secondary outcomes. There was a statistically significant higher responder rate for the off and on state in the opicapone 50 mg group when compared with placebo (70% versus 48%, odds ratio [OR] 2.5, 95% CI 1.5 to 4.3; $p=0.001$ and 65% versus 58%, OR 2.2, 95% CI 1.3 to 3.8; $p=0.003$). No statistically significant difference was found for entacapone when compared with placebo or with opicapone 50 mg for these outcomes ($p>0.05$).

The least squares mean difference in the total time in the on state at the end of the study when compared with placebo was found to be the greatest with opicapone 50 mg at 71.9 minutes (95% CI 35.0 to 108, $p=0.0001$), followed by entacapone at 52.6 minutes (95% CI 16.1 to 89.1, $p=0.005$). There was no statistically significant difference when opicapone 50 mg was compared with entacapone for this outcome ($p=0.30$).

Motor symptoms without troublesome dyskinesia

There was a statistically significant improvement in on time without troublesome dyskinesia by approximately 60 minutes with opicapone 50 mg when compared with placebo (95% CI 23.8 to 101.4, $p=0.002$). A statistically significant improvement was also seen for this outcome with entacapone when compared with placebo (47.6 minutes, 95% CI 9.3 to 6.0, $p=0.02$). There was no statistically significant difference when opicapone 50 mg was compared with entacapone for this outcome ($p=0.45$).

Clinician and patient global impression of change

The percentage of participants with any improvement from baseline in clinician global impression of change (CGI-C) and the patient global impression of change (PGI-C) was higher with opicapone groups compared with placebo and entacapone groups. A statistically significant difference was found in CGI-C with opicapone 50 mg when compared with placebo (73% versus 49.9%, $p=0.0005$). No statistically significant difference was found in CGI-C with entacapone when compared with placebo (50.9%, $p=0.61$). There was a statistically significant improvement in PGI-C with opicapone 50 mg when compared with placebo (72.1% versus 50.9%, $p=0.0008$). No statistically significant improvement was found with entacapone when compared with placebo (52.5%, $p=0.47$). Compared with entacapone, there was a statistically significant improvement in CGI-C and PGI-C with opicapone 50 mg ($p=0.007$ and $p=0.0091$ respectively).

Health-related quality of life, motor and daily activities scores

There was an improvement in health-related quality of life, motor scores and daily activities scores (assessed using UPDRS, PDSS, PDQ-39 and NMSS) from baseline to end point in all treatment groups (including placebo). The differences between active treatment (opicapone 50 mg and entacapone) and placebo groups were not statistically significant.

Changes in levodopa dosage

There was a decrease in the mean daily dose of levodopa therapy from baseline to end point in all treatment groups. This was the greatest for opicapone 50 mg (-31.6 mg) when compared with

placebo (-6.1 mg), however statistical significance was not reported. Entacapone reduced the mean daily levodopa dose by 14.5 mg.

An overview of the results for clinical effectiveness can be found in the [results tables](#).

BIPARK II study

An additional multicentre (including the UK) 14- to 15-week RCT ([Lees et al. 2016](#)) [BIPARK II] (n=427) study found that there was a statistically significant reduction in the time in [off state](#) by 54.3 minutes (95% CI -96.2 to -12.4, p=0.008) with opicapone 50 mg when compared with placebo. The study also reported findings from a 1-year open-label phase during which all participants received active treatment with opicapone (n=367). The participants started open-label treatment with 25 mg opicapone, which could be titrated up to 50 mg if greater symptom control was needed ([Lees et al. 2016](#)). The mean change in off time from the start to the end of the open-label phase was -18.31 minutes (95% CI -43.56 to +6.95) suggesting that the reduction in off time was sustained for 1 year.

Safety and tolerability

The [SPC](#) states that opicapone is contraindicated in people with pheochromocytoma, paraganglioma or other catecholamine secreting neoplasms. Opicapone is also contraindicated in people with a history of neuroleptic malignant syndrome and/or non-traumatic rhabdomyolysis.

Concomitant use with monoamine oxidase inhibitors (for example phenelzine, tranylcypromine and moclobemide) other than those for the treatment of Parkinson's disease is also contraindicated (SPC: opicapone). The SPC states that concomitant use with tricyclic antidepressants and noradrenaline re-uptake inhibitors should be considered with appropriate caution and co-administration with medicines metabolised by CYP2C8 such as repaglinide must be avoided. The SPC also states that concomitant use with safinamide should be considered with appropriate caution as there is no experience when used together.

The SPC states that it is often necessary to adjust the daily dose of levodopa within the first days to first weeks after starting treatment with opicapone to reduce levodopa-related dopaminergic adverse reactions such as dyskinesia.

In the BIPARK I study, safety outcomes were analysed for all participants who received at least 1 dose of the study medicine (n=599). The number of participants with treatment-emergent adverse events leading to discontinuation of opicapone 50 mg was 5 (4%), compared with 8 in the

placebo group (7%) and 8 in the entacapone group (7%). Diarrhoea, (2 in the entacapone group and 1 in the placebo group), visual hallucinations (1 in the opicapone 5 mg group, 2 in the opicapone 25 mg group, and 2 in the opicapone 50 mg group) and dyskinesia (2 in the opicapone 5 mg group) were common adverse events leading to treatment being discontinued. The number of participants experiencing at least 1 treatment-emergent adverse event was similar for all doses of opicapone and placebo (between 60 and 62 participants). The number of participants with serious treatment-emergent adverse events was the greatest for entacapone (n=8), followed by placebo (n=6) and opicapone 50 mg (n=4), statistical analysis was not reported.

Impulse control disorders can occur in people treated with dopamine agonists and/or other dopaminergic treatments. The SPC advocates regular monitoring for the development of impulse control disorders and review of treatment if symptoms develop. People taking dopaminergic treatments and their carers should be made aware of the behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating (SPC: opicapone).

In the BIPARK I study, impulse control disorders related to treatment were reported in 10 participants or fewer per group; opicapone 50 mg (n=8), entacapone (n=10) and placebo (n=5). The most commonly reported disorder in all groups was buying disorder (Ferreira et al. 2016).

The SPC for opicapone reports that dyskinesia is a very common adverse reaction occurring in 10/100 people or more. Common adverse reactions, occurring in 1/100 people or more, are dizziness, headache, somnolence, orthostatic hypotension, constipation, dry mouth, vomiting and muscle spasms.

In the BIPARK I study, dyskinesia was the most common reported treatment-emergent adverse event across treatment groups. This was most commonly reported with opicapone 50 mg (16%; n=18), when compared with entacapone (8%; n=10) and placebo (4%; n=5). Other adverse events affecting 5% or more participants taking opicapone included dizziness, insomnia and hallucinations (statistical analysis not reported). There was no increased suicidality in the opicapone or entacapone groups compared with placebo (Ferreira et al. 2016).

The [European public assessment report](#) (EPAR) includes results from the pooled analysis of BIPARK I and BIPARK II studies and states that the incidence of treatment-emergent serious adverse events was similar across the total opicapone (3.5%) and placebo (4.3%) groups (statistical analysis not reported).

An overview of the results for safety and tolerability can be found in the [results tables](#).

For full information see the [SPC for opicapone](#).

Evidence strengths and limitations

The RCT (BIPARK I) investigating the safety and efficacy of opicapone was a double-blind, placebo- and active-controlled study, which included a total of 600 participants across 106 centres in 19 European countries and Russia (Ferreira et al. 2016). The primary efficacy outcome measure was the reduced time in off state, which the EPAR for opicapone states is a valid and clinically relevant measure of efficacy.

The number of participants who withdrew from the treatment groups due to adverse events or for safety or ethical reasons were: placebo (n=9); entacapone (n=9); opicapone 5 mg (n=8); opicapone 25 mg (n=8); and opicapone 50 mg (n=6). The baseline participant clinical characteristics, demographics and treatment history were similar between the treatment groups. The active-control group received entacapone 200 mg with each levodopa dose. Entacapone is the most commonly used catechol-O-methyl transferase (COMT) inhibitor in practice for end-of-dose motor fluctuations and so was an appropriate comparator in the opicapone study. Masking of the opicapone and placebo was carefully maintained in the study and also the differences in frequency of administration of entacapone (up to 8 times each day) and opicapone (once daily) was taken into account as participants in the opicapone groups took placebo during the day with levodopa doses and active treatment as the bedtime dose (Ferreira et al. 2016).

Ferreira et al. (2016) used different study populations to test for superiority versus placebo (ITT analysis) and non-inferiority versus entacapone (per-protocol analysis). Both analyses support the efficacy of opicapone 50 mg compared with placebo and non-inferiority of opicapone 50 mg to entacapone. Based on the authors assuming a mean reduced off time from baseline to study end of 75 minutes for entacapone, a non-inferiority margin of 30 minutes was used to test for non-inferiority. Specialists involved in the production of this evidence summary commented that a non-inferiority margin of 30 minutes was appropriate to test for non-inferiority of opicapone with entacapone. The results of the primary outcome analysis were similar in the sensitivity analysis that was carried out. A mixed model was used for repeated measurements to take into account the study using a last observation carried forward method to adjust for missing data from the participant's diaries (Ferreira et al. 2016).

The EPAR for opicapone includes subgroup analysis on the primary efficacy outcome. It states that none of the subgroup analysis showed an interaction with the subgroup tested, indicating that results showing superiority of opicapone compared with placebo and non-inferiority to entacapone were consistent across all subgroups evaluated. Subgroup analysis included age, gender, modified

Hoehn and Yahr staging ([UPDRS V](#)) at baseline, levodopa formulation and daily dose, use of dopamine agonists and/or monoamine oxidase (MAO) inhibitors at baseline and different geographical areas.

Dose adjustments of levodopa were allowed between baseline and up to 3 weeks according to clinical response in the BIPARK I study, but the baseline dose was not to be exceeded and adjustments were not allowed after the first 3 weeks. This does not reflect routine practice, as the dose of levodopa can be adjusted when adjunctive therapy is started.

The BIPARK I study was carried out over a short period of up to 15 weeks and excluded a broad population of people with Parkinson's disease. Opicapone was investigated in mainly white people (mean age of approximately 64 years) with Parkinson's disease taking a stable optimised regimen of 3 to 8 daily doses of levodopa and other medicines for Parkinson's disease. People who had previously taken entacapone, had severe dyskinesia and/or severe or unpredictable periods in the off state, or both were excluded from the study. Some of the participants in the BIPARK I study were taking anticholinergics (5%) and medicines for Parkinson's disease that are not available in the UK. In the NICE guideline on [Parkinson's disease](#), anticholinergics are not included as an option for adjuvant therapy in people with later Parkinson's disease. Furthermore, the BIPARK I study was carried out in Europe (excluding the UK) and Russia, and participants may not reflect UK population and routine clinical practice.

An overview of the quality assessment of the included study can be found in the [evidence table](#).

Estimated impact for the NHS

Other treatments

A wide range of adjuvant treatments are available for people with Parkinson's disease who are experiencing end-of-dose motor fluctuations on levodopa alone, including other catechol-O-methyl transferase (COMT) inhibitors ([entacapone](#) and [tolcapone](#)). Entacapone is licensed for adjuvant therapy to levodopa/DOPA decarboxylase inhibitor (DDCI) in people with Parkinson's disease and end-of-dose motor fluctuations which cannot be stabilised on these combinations. Tolcapone is licensed for adjuvant therapy to levodopa/DDCI in people with Parkinson's disease and motor fluctuations, when other COMT inhibitors are not tolerated or when they have failed. Tolcapone is prescribed under specialist supervision only and needs frequent monitoring of liver function. Entacapone is commonly prescribed as a combination product, levodopa/carbidopa/entacapone ([Prescription cost analysis, England 2015](#)).

Alternative adjuvant options include dopamine agonists (for example, pramipexole, ropinirole and rotigotine) and monoamine oxidase-B (MAO-B) inhibitors (for example rasagiline, selegiline and safinamide).

Costs of other treatments

See table 3 for the costs of other COMT inhibitors.

Table 3 Costs of other treatments

Medicine/treatment	Usual dose	30-day cost, excluding VAT ^a
Entacapone 200 mg tablets ^b	200 mg taken with each levodopa/DDCI dose up to 10 times a day ^f	£50.30 ^{b, c}
Tolcapone 100 mg tablets (Tasmar)	100 to 200 mg 3 times a day as adjunct to levodopa ^d	£85.68 to £171.36 ^e

Abbreviation: DDCI, DOPA decarboxylase inhibitor.

^a Based on maximum daily dose, taken from the relevant [summary of product characteristics](#) (SPC). These directions do not represent the full range that can be used and they do not imply therapeutic equivalence.

^b Entacapone is also available as a combination preparation with different strengths of levodopa and carbidopa.

^c Costs taken from [Drug Tariff](#), February 2017 (excluding VAT).

^d The [SPC for tolcapone](#) states that the dose should only be increased to 200 mg 3 times a day in exceptional circumstances, when the anticipated incremental clinical benefit justifies the increased risk of hepatic reactions.

^e Costs taken from [MIMS](#), February 2017 (excluding VAT).

^f Specialists who commented on this evidence summary suggested that for most people, entacapone is taken between 4 and 7 times a day.

Current or estimated usage

The manufacturer estimates the number of people prescribed opicapone over the next 3 years will be 747 (2017), 1,748 (2018) and 2,982 (2019).

Likely place in therapy

Entacapone is the most prescribed COMT inhibitor as adjunctive therapy to levodopa and may be taken up to 10 times daily with each levodopa dose to manage end-of-dose motor fluctuations in Parkinson's disease. The use of tolcapone is limited because of the increased risk of hepatotoxicity and can only be prescribed and supervised by physicians experienced in the management of advanced Parkinson's disease (SPC: tolcapone). Opicapone is the third COMT inhibitor licensed in the UK as adjunctive therapy to levodopa in people with Parkinson's disease who are experiencing end-of-dose motor fluctuations. Opicapone is taken once a day, which enables a simplified regimen compared with entacapone, although combination preparations of entacapone/levodopa/DDCI are available and are frequently prescribed.

Specialists who reviewed this evidence summary highlighted that a combination product of entacapone may be difficult for some people who are on differing levodopa doses at different times of the day. Some people taking complicated dosing regimens may find it easier to add in a single tablet like opicapone and keep their familiar levodopa doses over the day. In addition, using a once-daily opicapone enables flexible dosing of levodopa without altering opicapone dose, unlike when using entacapone. Specialists who commented on this evidence summary suggested that opicapone may be an option to consider when entacapone is not tolerated or is inadequate at controlling symptoms. The majority of the participants in the study were taking additional medicines for Parkinson's disease such as dopamine agonists, monoamine oxidase inhibitors, anticholinergics and amantadine. Therefore, there are limited data on the use of opicapone as a first choice adjunctive therapy to levodopa.

Opicapone 50 mg showed efficacy in the primary outcome measure and also in most secondary outcomes including clinician and patient [global assessment of change](#) (see [clinical effectiveness](#)). The magnitude of effect of opicapone 50 mg with a reduced [off time](#) of 60.8 minutes and an increase in [on time](#) without troublesome dyskinesia of 62.6 minutes compared with placebo was considered clinically relevant and moderate ([European public assessment report \[EPAR\]: opicapone](#)). The duration of time in the on state with troublesome dyskinesia did not change. Opicapone 50 mg was shown to be non-inferior to entacapone 200 mg for improving motor fluctuations and indicated a greater reduced off time compared with entacapone.

The EPAR for opicapone states that the daily dose of 50 mg has proven to be consistently efficacious. BIPARK I demonstrated efficacy of opicapone 50 mg in up to 15 weeks only. Reduction in off time was sustained for 1 year with opicapone 25 mg to 50 mg in an open-label study ([Lees et al. 2016](#); BIPARK II). The incidence of serious treatment-emergent adverse events with opicapone did not differ from that in the placebo or entacapone groups ([Ferreira et al. 2016](#)). The most

common adverse events reported with opicapone were dyskinesia, constipation, insomnia and dry mouth. The EPAR for opicapone states that dyskinesias were reported in more than 10% of participants receiving opicapone in which case it may be necessary to reduce the levodopa dose within the first days to first weeks after starting opicapone to prevent severe dyskinesias.

In addition to effectiveness, safety and patient factors, local decision-makers will need to take cost into account when considering the likely place in therapy of opicapone. Opicapone is more expensive than entacapone, which is the most commonly prescribed COMT inhibitor: 30-day treatment costs (excluding VAT) for: opicapone 50 mg is £93.90 ([MIMS](#), February 2017); entacapone based on maximum dose is £50.30 ([Drug Tariff](#), February 2017); and tolcapone based on 100 mg dose is £85.68 (MIMS, February 2017).

The NICE guideline on [Parkinson's disease](#) makes recommendations on the place in therapy of adjuvant treatments, including COMT inhibitors (see [introduction and current guidance](#)). The choice of treatment will depend on the person's clinical and lifestyle characteristics, and their preferences, after an informed discussion about the benefits and risks of treatment.

Information for the public about medicines

Evidence summaries provide an overview of the best evidence that is available about specific medicines. They also give general information about the condition that the medicine might be prescribed for, how the medicine is used, how it works, and what the aim of treatment is.

Evidence summaries aim to help healthcare professionals and patients decide whether medicines are safe to use and if they are likely to work well, especially when there isn't another suitable medicine that has a licence for the condition. They don't contain recommendations from NICE on whether the medicine should be used.

Information about licensing of medicines

In the UK, medicines need to have a licence before they can be widely used. To get a licence, the manufacturer of the medicine has to provide evidence that shows that the medicine works well enough and is safe enough to be used for a specific condition and for a specific group of patients, and that they can manufacture the medicine to the required quality. Evidence summaries explain whether a medicine has a licence, and if it does what the licence covers.

There is more information about licensing of medicines on [NHS Choices](#).

Medicines can be prescribed if they don't have a licence (unlicensed) or for 'off-label' use. Off-label means that the person prescribing the medicine wants to use it in a different way than that stated in its licence. This could mean using the medicine for a different condition or a different group of patients, or it could mean a change in the dose or that the medicine is taken in a different way. If a healthcare professional wants to prescribe an unlicensed medicine, or a licensed medicine off-label, they must follow their professional guide, for example for doctors the General Medical Council's [good practice guidelines](#). These include giving information about the treatment and discussing the possible benefits and harms so that the person has enough information to decide whether or not to have the treatment. This is called giving informed consent.

Questions that might be useful to ask about medicines

- Why am I being offered this medicine?
- Why am I being offered a medicine that is being used off-label?
- What does the treatment involve?
- What are the benefits I might get?
- How good are my chances of getting those benefits?
- Could having the treatment make me feel worse?
- Are there other treatments I could try?
- What are the risks of the treatment?
- Are the risks minor or serious? How likely are they to happen?
- What could happen if I don't have the treatment?

Relevance to other NICE programmes

NICE issued a guideline on [Parkinson's disease](#) in June 2006. This is currently being [updated](#) (publication expected April 2017).

This use of opicapone is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

References

Ferreira J, Lees A, Rocha JF et al. (2016) Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomised, double-blind, controlled trial. *The Lancet Neurology* 15(2), 154–65

Lees AJ, Ferreira J, Rascol O et al. (2016) Opicapone as adjunct to levodopa therapy in patients with Parkinson disease and motor fluctuations. A randomized clinical trial. *Journal of American Medical Association Neurology*. Published online. doi:10.1001/jamaneurol.2016.4703

Peto V, Jenkinson C, Fitzpatrick R. (2001) Determining minimally important differences for the PDQ-39 Parkinson's disease questionnaire. *Age and Ageing* 30(4), 299–302

Schrag A, Sampaio C, Counsell N et al. (2006) Minimal clinically important change on the unified Parkinson's disease rating scale. *Movement disorders* 21(8), 1200–07

Shulman L, Gruber-Baldini A, Anderson K, et al. (2010) The clinically important difference on the unified Parkinson's disease rating scale. *JAMA Neurology* 67, 64–70

Evidence table

Table 4 Ferreira J et al. 2016 (BIPARK I)

Study reference	Ferreira JJ, Lees A, Rocha JF, et al. (2016) <u>Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomised, double-blind, controlled trial</u> <i>The Lancet Neurology</i> 15(2), 154–65
Unique identifier	<u>NCT01568073, EudraCT2010-021860-13</u>
Study type	RCT
Aim of the study	To assess the safety and efficacy of opicapone as an adjunct to levodopa compared with placebo or entacapone in people with Parkinson's disease and motor fluctuations
Study dates	Between March 2011 and November 2013

Setting	106 specialist centres across 19 European countries (excluding the UK) and Russia
Number of participants	n=600 randomised
Population	Aged 30 to 83 years with Parkinson's disease with end-of-dose motor fluctuations on a stable optimised dose of levodopa and other medicines for Parkinson's disease Participant's demographics, baseline Parkinson's disease characteristics and treatment history did not differ between the different groups
Inclusion criteria	Clinical diagnosis of Parkinson's disease of at least 3 years' duration; Hoehn and Yahr stage 1 to 3 during <u>on time</u> ; at least 1 year of clinical improvement with levodopa treatment; on a stable optimised treatment of 3 to 8 daily doses of levodopa and other Parkinson's disease medicines for at least 4 weeks before screening; signs of end-of-dose motor fluctuations for at least 4 weeks before screening; mean total awake time in the off state of at least 1.5 hours, not including morning akinesia. Participants also had to be able to keep reliable diaries of motor fluctuations
Exclusion criteria	Previous treatment with entacapone; a dyskinesia disability score >3 on item 33 (disability) of the <u>UPDRS</u> ; severe or unpredictable periods in the <u>off state</u> , or both; previous surgery or deep brain stimulation for Parkinson's disease; history of neuroleptic malignant syndrome or non-traumatic rhabdomyolysis; concomitant use of tolcapone, apomorphine, entacapone (other than that supplied in the study), neuroleptics, venlafaxine, MAO inhibitors (except selegiline up to 10 mg/day orally or up to 1.25 mg/day buccal and rasagiline up to 1 mg/day) or anti-emetics with antidopaminergic action (except domperidone). Participants with clinically significant unstable cardiovascular disease, psychiatric illness or any other medical condition that increase risks were also excluded
Intervention(s)	<ul style="list-style-type: none"> • Opicapone 5 mg once at night (n=122) • Opicapone 25 mg once at night (n=119) • Opicapone 50 mg once at night (n=116)

Comparator(s)	2 comparators: <ul style="list-style-type: none"> • Placebo (n=121) • Entacapone 200 mg with each levodopa dose (n=122)
Length of follow-up	14 to 15 weeks. The participants visited the investigators 7 times: visit 1, screening; visit 2, randomisation (baseline); visit 3, 1 week after baseline; visit 4, depended on need for levodopa adjustment (between 2 and 3 weeks after baseline); thereafter assessments occurred at 4-week intervals for visits 5, 6 and 7
Outcomes	Primary outcome: <ul style="list-style-type: none"> • Mean change from baseline to study end in absolute time in the off state, assessed by daily paper participant diaries

	<p>Secondary outcomes:</p> <ul style="list-style-type: none">• Change in the proportion of participants achieving at least 1 hour reduction in absolute time in the off state• Change in the proportion of participants achieving at least 1 hour increase in absolute total time in the on state• Total time in on state at the end of the study treatment• Total time in on state without troublesome dyskinesia• Total time in on state with troublesome dyskinesia• Percent of time in the off state• Percent of time in the on state• Percent of time in on state without troublesome dyskinesia• Percent of time in on state with troublesome dyskinesia• <u>UPDRS</u> total score• <u>PDSS</u> score• <u>PDQ-39</u> score• <u>NMSS</u> score• <u>CGI-C</u> score• <u>PGI-C</u> score
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	<p>Safety outcomes:</p> <ul style="list-style-type: none"> • Percentage of participants with at least 1 TEAE • Percentage of participants with TEAE's leading to study medicine discontinuation • Number of serious TEAEs • Number of serious TEAEs possibly related to treatment <p>ECG recordings and physical, neurological and dermatological examinations were done at baseline and at the end of the double-blind period (visit 7). Standard laboratory safety tests, the Columbia suicide severity rating scale, and the modified Minnesota impulsive disorder interview were done at baseline and visits 4 to 7</p>	
Source of funding	BIAL	
Overall risk of bias/quality assessment (CASP RCT checklist)	Did the trial address a clearly focused issue?	Yes
	Was the assignment of patients to treatments randomised?	Yes
	Were patients, health workers and study personnel blinded?	Yes ^a
	Were the groups similar at the start of the trial?	Yes
	Aside from the experimental intervention, were the groups treated equally?	Yes ^b
	Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
	How large was the treatment effect?	See table 5
	How precise was the estimate of the treatment effect?	See table 5
	Can the results be applied in your context? (or to the local population)	Unclear ^c
	Were all clinically important outcomes considered?	Yes

	Are the benefits worth the harms and costs?	See key points
Study limitations	<ul style="list-style-type: none"> • The study excluded a broad population of participants such as those with severe or unpredictable off episodes or with severe dyskinesia. • Study only designed to assess the effect of opicapone in people with end-of-dose wearing off which is characterised by predictability of 'off' episodes. • Short study duration of 14 to 15 weeks. • Different study populations used to test for the superiority of opicapone versus placebo (full analysis set) and non-inferiority of opicapone versus entacapone (per-protocol set). 	
Comments	<p>^a Participants were randomly assigned (1:1:1:1) at baseline using a computer-generated scheme to each study arm using blocks of 8 to 10 depending on regimen stratified by centre. Participants and investigators were masked to treatment throughout the study</p> <p>^b There were 3 main population sets: intention-to-treat analysis (full set) included all randomly assigned participants who took at least 1 dose of study medicine and had at least 1 assessment of time in the off state after baseline; per-protocol set included all participants in the full analysis set who did not majorly deviate from the protocol and; safety set included all participants who received at least 1 dose of study medicine</p> <p>^c There were no UK centres used in the study. The study was conducted in Austria (n=3), Bosnia-Herzegovina (n=16), Bulgaria (n=50), Croatia (n=14), Czech Republic (n=51), France (n=15), Germany (n=35), Hungary (n=10), Italy (n=14), Latvia (n=7), Lithuania (n=15), Poland (n=90), Portugal (n=22), Romania (n=53), Russia (n=34), Serbia (n=36), Slovakia (n=19), Spain (n=37) and Ukraine (n=79)</p> <p>Opicapone enhances the effects of levodopa so the daily dose of levodopa was reduced (but not frequency) between baseline and up to 3 weeks according to clinical response</p>	

Abbreviations: CGI-C, clinician global impression of change; DDCI, DOPA decarboxylase inhibitor; MAO, monoamine oxidase; NMSS, non-motor symptoms scale; PDQ-39, 39-item Parkinson's disease questionnaire; PDSS, Parkinson's disease sleep scale; PGI-C, patient global impression of change; RCT, randomised controlled trial; SD, standard deviation; UPDRS, unified Parkinson's disease rating scale; TEAE; treatment-emergent adverse event.

Results tables

Table 5 Ferreira J et al. 2016 (BIPARK I)

	Placebo	Opicapone 50 mg	Entacapone 200 mg	Analysis
n (full analysis set) ^a	120	115	120	
Primary outcome				
Adjusted least squares mean change from baseline in absolute time (mins) in the <u>off state</u>	-56.0 (from a baseline of 6.2 hours)	-116.8 (from a baseline of 6.2 hours)	-96.3 (from a baseline of 6.5 hours)	Mean difference vs placebo (95% CI) ^b
				Opicapone 50 mg: -60.8 mins (-97.2 to -24.4), p=0.0015
				Entacapone 200 mg: -40.3 mins (-76.2 to -4.3), p=0.014
				Mean difference between entacapone 200 mg vs opicapone 50 mg (95% CI) ^{c,d}
				-26.2 mins (-63.8 to 11.4), p=0.0051
Selected secondary outcomes				

Number of participants achieving a 1 hour or more reduction in absolute time in the off state	57/120 (48%)	80/115 (70%)	70/120 (58%)	Comparison with placebo <u>OR</u> (95% CI) Opicapone 50 mg: 2.5 (1.5 to 4.3), p=0.001 Entacapone 200 mg: 1.6 (0.9 to 2.6), p=0.094, NS
Number of participants achieving a 1 hour or more increase in the absolute time in the on state	55/120 (46%)	75/115 (65%)	69/120 (58%)	Comparison with placebo OR (95% CI) Opicapone 50 mg: 2.2 (1.3 to 3.8), p=0.003 Entacapone 200 mg: 1.6 (1.0 to 2.7), p=0.067, NS
Least squares mean change in total time (mins) in the <u>on state</u> to study end	47.1 (from a baseline of 10 hours)	119.0 (from a baseline of 9.9 hours)	99.7 (from a baseline of 9.6 hours)	Mean difference vs placebo (95% CI) Opicapone 50 mg: 71.9 (35.0 to 108.8), p=0.0001 Entacapone 200 mg: 52.6 (16.1 to 89.1), p=0.005
Least squares mean change in time (mins) in the on state without troublesome dyskinesia	46.5	109.1	94.1	Mean difference vs placebo (95% CI) Opicapone 50 mg: 62.6 (23.8 to 101.4), p=0.002 Entacapone 200 mg: 47.6 (9.3 to 6.0), p=0.02

Least squares mean change in the <u>UPDRS</u> total score from baseline to study end ^e	-5.4	-6.1	-6.1	p value vs placebo ^f Opicapone 50 mg, p=0.56, NS Entacapone 200 mg, p=0.56, NS
Least squares mean change in the <u>PDSS</u> score from baseline to study end ^g	1.0	2.9	2.9	p value vs placebo ^f Opicapone 50 mg, p=0.45, NS Entacapone 200 mg, p=0.45, NS
Least squares mean change in the <u>PDQ-39</u> total score from baseline to study end ^h	-2.6	-2.8	-4.0	p value vs placebo ^f Opicapone 50 mg, p=0.90, NS Entacapone 200 mg, p=0.28, NS
Least squares mean change in the <u>NMSS</u> score from baseline to study end ⁱ	-5.7	-2.0	-4.7	p value vs placebo ^f Opicapone 50 mg, p=0.06, NS Entacapone 200 mg, p=0.63, NS
<u>CGI-C</u> (% of patients with improvement) ^j	49.9	73	50.9	p value vs placebo ^f Opicapone 50 mg, p=0.0005 Entacapone 200 mg, p=0.61, NS
<u>PGI-C</u> (% of patients with improvement) ^j	50.9	72.1	52.5	p value vs placebo ^f Opicapone 50 mg, p=0.0008 Entacapone 200 mg, p=0.47, NS
Safety and tolerability outcomes				
n (safety set)	121	115	122	

Number of participants with at least 1 TEAEs	60/121 (50%)	62/115 (54%)	69/122 (57%)	Not reported
Number of participants with TEAEs leading to study medicine discontinuation	8/121 (7%)	5/115 (4%)	8/122 (7%)	Not reported
Number of participants with TEAEs	6/121 (5%)	4/115 (3%)	8/122 (7%)	Not reported
Number of participants with dyskinesia	5/121 (4%)	18/115 (16%)	10/122 (8%)	Not reported
<p>^a <u>Intention-to-treat analysis</u> (full analysis set)</p> <p>^b Superiority test vs placebo</p> <p>^c Non-inferiority test vs entacapone (non-inferiority margin of 30 minutes)</p> <p>^d <u>Per protocol</u> set: entacapone 200 mg, n=104; opicapone 50 mg, n=106, see <u>EPAR</u> for details.</p> <p>^e Analysed in 114 participants in the placebo group, 109 in the opicapone 50 mg group and 111 in the entacapone group</p> <p>^f Effect size not reported in the paper</p> <p>^g Analysed in 117 participants in the placebo group, 112 in the opicapone 50 mg group and 118 in the entacapone group</p> <p>^h Analysed in 120 patients in the placebo group, 113 in the opicapone 50 mg group and 117 in the entacapone group</p> <p>ⁱ Analysed in 118 patients in the placebo group, 112 in the opicapone 50 mg group and 116 in the entacapone group</p> <p>^j Data for 3 participants in the entacapone group and for 2 participants in the opicapone group were missing or they were not assessed</p> <p>Abbreviations: CGI-C, clinician global impression of change; CI, confidence interval; NS, not statistically significant; OR, odds ratio; PGI-C, patient global impression of change; TEAE, treatment-emergent adverse event.</p>				

Excluded studies

No studies were excluded in the second sift.

Terms used in this evidence summary

Clinician global impression of change (CGI-C)

The clinician global impression of change (CGI-C) measures the change in clinician global impression relative to a baseline state at the beginning of the study. This change is rated as: very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse. Patients with 'improvement' are those rated as very much improved, much improved or minimally improved.

Non-motor symptom scale (NMSS)

The non-motor symptom scale assesses non-motor symptoms that may be associated with Parkinson's disease. This consists of 30 questions for the patients to answer yes or no to. Points are scored out of 30. Scores that are 10 or lower indicates mild, 10 to 20 indicated moderate and over 20 indicates severe ([Parkinson's UK](#)).

On and off time

People with Parkinson's disease can experience motor fluctuations (particularly when the dose of levodopa begins to wear off), which they often describe as being turned 'on' and 'off'. On and off time was recorded in participant diaries in the RCTs. Participants reported whether they were: 'on' with no dyskinesia, 'on' with no troublesome dyskinesia (not interfering with function or causing meaningful discomfort), 'on' with troublesome dyskinesia, 'off' (lack of mobility [bradykinesia or akinesia]), or asleep.

Parkinson's disease questionnaire (PDQ-39)

The Parkinson's disease questionnaire (PDQ-39) is a 39-item patient-reported rating scale that measures Parkinson's disease-specific, health-related quality of life. It covers 8 areas: mobility, activities of daily living (ADL), emotional wellbeing, stigma, social support, cognition, communication and bodily discomfort. Lower scores indicate better health-related quality of life. PDQ-39 total scores range from 0 to 800 (personal communication: Bial January 2017). The total score can be summarised into the PDQ-39 summary index score (range of scores 0 to 100). See [Peto et al. \(2001\)](#) for more information.

Parkinson's disease sleep scale (PDSS)

The Parkinson's disease sleep scale allows health and social care practitioners and people with Parkinson's disease to self-rate and quantify the level of sleep disruption being experienced in order to target treatment appropriately. It consists of 15 questions for the person to answer on a scale of 0 to 10, 0 for awful or always and 10 for excellent or never ([Parkinson's UK](#)).

Patient global impression of change (PGI-C)

The patient global impression of change (PGI-C) measures the change in the person's global impression relative to a baseline state at the beginning of the study. This change is rated as: very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse. People with 'improvement' are those rated as very much improved, much improved or minimally improved.

UPDRS

UPDRS is the unified Parkinson's disease rating scale used to assess symptoms associated with Parkinson's disease. It consists of: mentation, behaviour and mood (I); activities of daily living (II); motor examination (III); complications of therapy (IV); modified Hoehn and Yahr staging (V); and Schwab and England scale (VI). The questions can be answered in the on or off state. Lower scores are better. See [Shrag et al \(2006\)](#) and [Shulman et al. \(2010\)](#) for more information.

Search strategy

Medline (1996-present)

Search date: 12th October 2016

1 Opicapone.mp. or opicapone/ (14)

2 Ongentys.tw. (0)

3 ("BIA 9-1067" or BIA91067 or "BIA9-1067").tw. (4)

4 or/1-3 (14)

5 (NCT01227655 or NCT01568073).tw. (0)

6 ("NCT 01227655" or "NCT 01568073").tw. (0)

7 4 or 5 or 6 (14)

Medline in-process, In-Process & Other Non-Indexed Citations 7th October, 2016

Search date: 12th October 2016

1 Opicapone.mp. or opicapone/ (7)

2 Ongentys.tw. (1)

3 ("BIA 9-1067" or BIA91067 or "BIA9-1067").tw. (0)

4 or/1-3 (7)

5 (NCT01227655 or NCT01568073).tw. (0)

6 ("NCT 01227655" or "NCT 01568073").tw. (0)

7 4 or 5 or 6 (7)

Embase (1996 to 2016 Week 41)

Search date: 12th October 2016

1 Opicapone.mp. or opicapone/ (115)

2 Ongentys.tw. (1)

3 ("BIA 9-1067" or BIA91067 or "BIA9-1067").tw. (9)

4 or/1-3 (120)

5 *randomized controlled trial/ (37203)

6 *Randomization/ (1537)

7 *Placebo/ (23986)

8 *Crossover Procedure/ (3672)

9 (random or randomi* or randoml*).tw. (998741)

10 rct*.tw. (42634)

11 (phase 4 or phase iv or phase 3 or phase iii).tw. (63281)

12 placebo*.tw. (196243)

13 (crossover* or (cross adj over*)).tw. (64127)

14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (1118891)

15 Nonhuman/ (3541030)

16 Human/ (12718556)

17 15 not (15 and 16) (2399254)

18 14 not 17 (1032878)

19 4 and 18 (79)

20 (NCT01568073 or NCT01227655).tw. (1)

21 ("NCT 01227655" or "NCT 01568073").tw. (0)

22 or/19-21 (79)

23 conference.af. (2859472)

24 22 not 23 (14)

Cochrane/CRD databases

Search date: 12th October 2016

#1 opicapone:ti,ab,kw 50

#2 BIA 9-1067 0

#3 BIA91067 0

#4 BIA9-1067 0

#5 Ongentys 0

Development of this evidence summary

The [evidence summary: process guide](#) (2017) sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

Dr Christopher Kobylecki: honoraria for delivering educational meetings (content developed independently) from Ipsen, UCB Pharma; travel support to attend international meetings from Britannia Pharmaceuticals; honoraria for teaching from Teva Pharmaceuticals.

Dr Hilary Tyne: honorarium from UCB pharma for giving an educational talk; received November 2016.

About this evidence summary

Evidence summaries provide a summary of the best available published evidence for selected new medicines, unlicensed medicines or off-label use of licensed medicines.

The summaries assess the strengths and weaknesses of the best available evidence to inform health professionals and commissioners' decision-making.

This summary is not NICE guidance.

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