LMMG New Medicine Recommendation

Opicapone 50mg hard capsules for use in adult patients with Parkinson's disease with "end of dose" motor fluctuations who cannot be stabilised on levodopa/DDCI inhibitors

LMMG Recommendation:

AMBER0: Opicapone is recommended as a second line catechol-o-methyltransferase [COMT] inhibitor in adult patients with Parkinson's disease with "end of dose" motor fluctuations who cannot be stabilised on levodopa/DDCI inhibitors and who fail to respond to or are intolerant of entacapone, where tolcapone is being considered.

Introduction

Opicapone was identified by the horizon scanning process and considered at the January 2017 LMMG meeting. Following discussions, the LMMG agreed a "Black" RAG status for opicapone as the group felt that there was insufficient evidence to demonstrate opicapone would be either more effective or better tolerated than entacapone. It was also felt that the drug is more expensive than entacapone and a favourable cost/benefit profile could not be calculated for the drug. The original evidence review is presented in appendix 1, below.

Following correspondence from a specialist at LTHT received in April 2017, the LMMG were requested to review the decision to assign opicapone a "Black" RAG status. The request for re-review was prompted by the March 2017 publication of a NICE Evidence Summary [1] for opicapone and the specialist's view on the place of opicapone in the treatment pathway. The group decided there was insufficient new evidence to warrant a re-review of opicapone and advised that a re-review would be undertaken, only if there was anything materially different in the NICE clinical guideline update for the management of Parkinson's disease.

At the July 2018 meeting of the LMMG, it was agreed that the RAG status of opicapone could be re-reviewed following a further request from the specialist at LTHT.

Background

Opicapone is a peripheral, selective and reversible catechol-O-methyltransferase (COMT) inhibitor and 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 levodopa/DDCI inhibitors. [2]

The recommended dose of opicapone is 50 mg as an adjunct to levodopa/DDCI inhibitors. Opicapone should be taken once-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. [2]

Justifications for reclassification of opicapone to Amber0

1. **Safety: Opicapone provides an alternative second line COMT inhibitor agent in addition to tolcapone**
2. **Place of opicapone in the treatment pathway**
3. **Interpretation of the evidence presented at the January 2017 meeting of the LMMG**
4. **Approval and subsequent prescribing in other health economies**
5. **Additional justifications for the use of opicapone**

1. Safety: Opicapone provides an alternative second line COMT inhibitor agent in addition to tolcapone

There are currently three COMT inhibitors which are licensed as an adjunct to co-beneldopa or co-careldopa in Parkinson's disease with "end of dose" motor fluctuations. These are entacapone (also available in combination products), tolcapone and opicapone. Currently the LMMG recommends the use of entacapone ("Amber0") and tolcapone ("Red"), but not opicapone. Entacapone is accepted by specialists as the first line COMT inhibitor, however where patients are intolerant or unresponsive to entacapone, the only available alternative COMT inhibitor across the local health economy is tolcapone.

The summary of product characteristics for tolcapone states that it should only be used in the management of advanced Parkinson's disease following complete informative discussions of its risks with the patient. This is due to the risk of rare but potentially fatal acute liver injury. During treatment with tolcapone, liver function should be monitored every two weeks of the first year of therapy, every four weeks for the next six months, then every eight weeks thereafter. Isolated cases consistent with neuroleptic malignant syndrome have also been associated with tolcapone treatment. The SPC for Tamsar (branded tolcapone) has a boxed warning as follows: [3]

Tasmar therapy should only be initiated by physicians experienced in the management of advanced Parkinson's disease, to ensure an appropriate risk-benefit assessment. Tasmar should not be prescribed until there has been a complete informative discussion of the risks with the patient.

Tasmar should be discontinued if substantial clinical benefits are not seen within 3 weeks of the initiation of the treatment regardless of dose.

Liver Injury:

Because of the risk of rare but potentially fatal acute liver injury, Tasmar is only indicated for use in patients with levodopa-responsive idiopathic Parkinson's disease and motor fluctuations, who failed to respond to or are intolerant of other COMT inhibitors. Periodic monitoring of liver enzymes cannot reliably predict the occurrence of fulminant hepatitis. However, it is generally believed that early detection of medicine-induced hepatic injury along with immediate withdrawal of the suspect medication enhances the likelihood for recovery. Liver injury has most often occurred between 1 month and 6 months after starting treatment with Tasmar. Additionally late onset hepatitis after approximately 18 months of treatment has been reported rarely.

It should also be noted that female patients may have a higher risk of liver injury

Before starting treatment: If liver function tests are abnormal or there are signs of impaired liver function, Tasmar should not be prescribed. If Tasmar is to be prescribed, the patient should be informed about the signs and symptoms which may indicate liver injury, and to contact the physician immediately.

During treatment: Liver function should be monitored every 2 weeks for the first year of therapy, every 4 weeks for the next 6 months and every 8 weeks thereafter. If the dose is increased to 200 mg tid, liver enzyme monitoring should take place before increasing the dose and then be reinitiated following the sequence of frequencies as above. Treatment should be immediately discontinued if ALT and/or AST exceed the upper limit of normal or if symptoms or signs suggesting the onset of hepatic failure (persistent nausea, fatigue, lethargy, anorexia, jaundice, dark urine, pruritus, right upper quadrant tenderness) develop.

If treatment is discontinued: Patients who show evidence of acute liver injury while on Tasmar and are withdrawn from the medicinal product may be at increased risk for liver injury if Tasmar is re-introduced. Accordingly, such patients should not be considered for retreatment.

Neuroleptic Malignant Syndrome (NMS):

In Parkinson`s patients, NMS tends to occur when discontinuing or stopping dopaminergic-enhancing medications. Therefore, if symptoms occur after discontinuing Tasmar, physicians should consider increasing the patient's levodopa dose

Isolated cases consistent with NMS have been associated with Tasmar treatment. Symptoms have usually onset during Tasmar treatment or shortly after Tasmar has been discontinued. NMS is characterised by motor symptoms (rigidity, myoclonus and tremor), mental status changes (agitation, confusion, stupor and coma), elevated temperature, autonomic dysfunction (labile blood pressure, tachycardia) and elevated serum creatine phosphokinase (CPK) which may be a consequence of myolysis. A diagnosis of NMS should be considered even if not all the above findings are present. Under such a diagnosis Tasmar should be immediately discontinued and the patient should be followed up closely.

Before starting treatment: To reduce the risk of NMS, Tasmar should not be prescribed for patients with severe dyskinesia or a previous history of NMS including rhabdomyolysis or hyperthermia. Patients receiving multiple medications with effects on different central nervous system (CNS) pathways (e.g. antidepressants, neuroleptics, anticholinergics) may be at greater risk of developing NMS.

According to the European Public Assessment Report for opicapone, “there are no major safety concerns” and most adverse events are comparable to other COMT inhibitors. [4] Opicapone would therefore be suitable for prescribing in primary care following initiation and titration of the levodopa dose by a specialist.

2. Place of opicapone in the treatment pathway

The consultation responses received from the three LMMG members who did not support the “Amber0” recommendation for opicapone cited lack of evidence of a place in the treatment pathways for opicapone.

Both local specialists and national guidance from a NICE evidence summary [1] have since proposed a place in therapy for opicapone. A local specialist has submitted a pathway demonstrating that opicapone has a place in therapy as a second line agent for patients who:

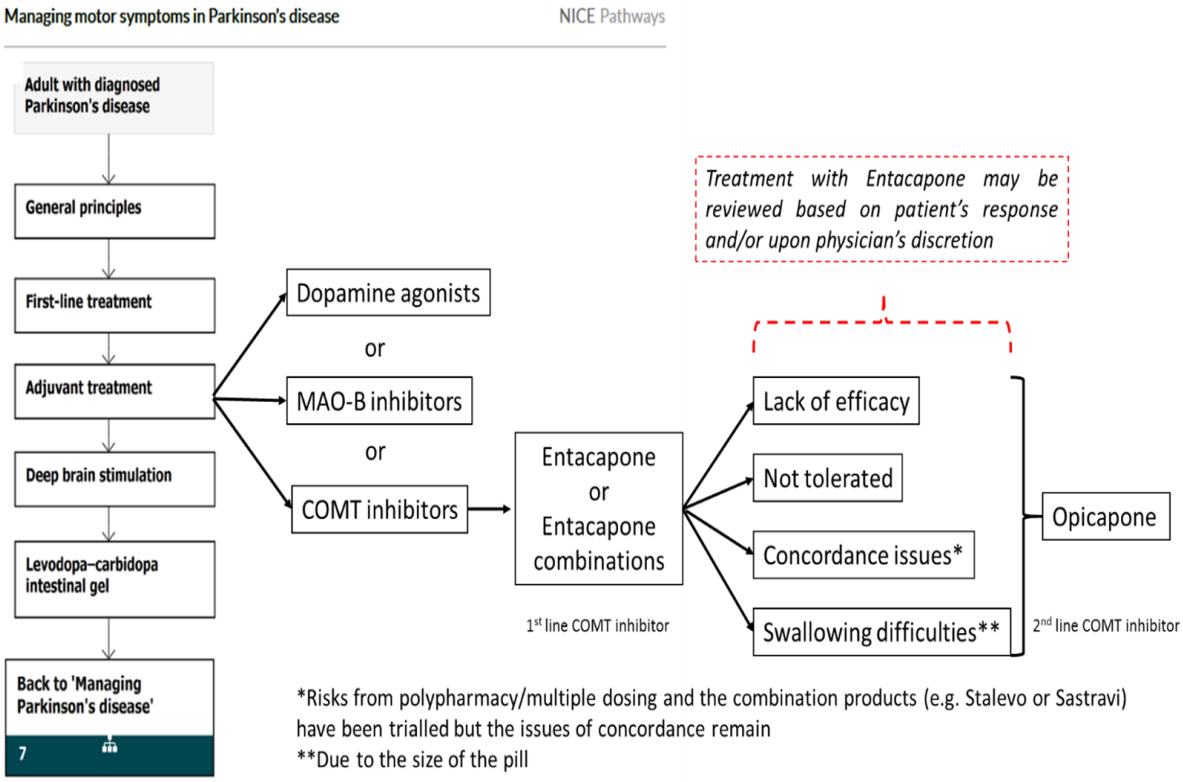
- fail to respond adequately to entacapone or
- cannot tolerate entacapone or
- have concordance issues or
- experience swallowing difficulties with entacapone (see figure 1 below).

This pathway is supported by:

- Dr.Rejith Dayanandan Consultant Neurology, Central & North Lancashire area and Clinical director Neurology Department;
- Dr.Sandeep Shaunak, Consultant Neurology, Central & East Lancashire area;
- Dr.Tahir Majeed, Consultant Neurology, Central Lancashire;
- Prof. Suresh Chhetri, Consultant Neurology, Central and East Lancashire;
- Dr.Omesh Kulkarni, Consultant Neurology, Parkinson's and Movement Disorders lead for Central Lancashire, Blackpool and Fylde coast.

At a national level, specialists who commented on the NICE evidence summary suggested that opicapone may be an option to consider when entacapone is not tolerated or is inadequately controlling symptoms. [1]

Figure 1: Parkinson's Treatment Pathway, focus on COMT inhibitors



Adapted from: https://www.nice.org.uk/guidance/ng71

3. Interpretation of the evidence at the January 2017 meeting of the LMMG

The minutes of the January 2017 LMMG meeting state:

"the group felt that there was no evidence of additional benefit compared to entacapone. Additionally, there was no evidence to show that this would be better tolerated for patients who are unable to tolerate entacapone. The group therefore did not agree with the recommendation but agreed on a Black colour classification." The following bullet points expand on the objections raised at the initial consultation:

- *"no evidence of additional benefit"* – The LMMG evidence review summarises that opicapone demonstrated non-inferiority but not superiority to entacapone in terms of change from baseline in OFF time in the BIPARKI pivotal study. [5] However the consensus from specialists both locally and nationally (amongst those who commented on the NICE evidence summary), is that opicapone can provide additional benefit when patients: fail to respond adequately to or cannot tolerate entacapone; have concordance issues; or experience swallowing difficulties. There is also evidence from an unpublished post-hoc analysis of the BIPARKI that patients taking placebo or entacapone showed statistically significant reduction in the OFF time and increase in the ON time without troublesome dyskinesia after switching to opicapone. [6]
- *"no evidence to show that this would be better tolerated for patients who are unable to tolerate entacapone"* – The original LMMG evidence review stated that "the safety and tolerability of opicapone is generally good and the majority of adverse events are comparable to other COMT inhibitors as stated by the EMEA". The NICE evidence summary also states that "opicapone was well tolerated with a relatively low incidence of adverse events compared with placebo and entacapone".

4. Approval and subsequent prescribing in other health economies

Many of the health economies surrounding Lancashire and South Cumbria have now approved opicapone 50mg, including Pan-Mersey, GMMMG and North Cumbria APC. All these health economies have reviewed and approved opicapone 50mg in a 2nd line position to entacapone (or triple therapy combinations including entacapone). Although the LMMG is not obligated to approve the use of new medicines in line with other bordering health economies, the disparity between the LMMG position and that of Pan-Mersey, GMMMG and North Cumbria APC may complicate treatment pathways in those referred back from tertiary services and may be perceived to create an inequity for the patients of Lancashire.

Prescribing data from ePACT for the 12 months to May 2018 for two areas which have approved the use of opicapone as an "Amber" medicine is detailed below (figure 2).

Figure 2: ePACT data, COMT inhibitors, 12 months

Merseyside

	Values	
BNFChemicalSubstance	Prescriber Act Cost	Prescriber Items
Entacapone	£7,862.10	619
Levodopa/Carbidopa/Entacapone	£239,159.90	4595
Opicapone	£3,947.12	44

Midlands and Surrounds

	Values	
BNFChemicalSubstance	Prescriber Act Cost	Prescriber Items
Entacapone	£24,039.68	1755
Levodopa/Carbidopa/Entacapone	£398,309.48	6805
Opicapone	£26,950.80	277
Tolcapone	£964.60	13

Prescribing data shows a small amount of opicapone prescribing in the year to May 2018, however entacapone and its combination products account for 97%-99% of all COMT inhibitors dispensed from primary care in this timeframe.

5. Additional justifications for the use of opicapone

- **Choice – The NICE guideline for Parkinson's disease in adults (NG71) states:**

  "*Offer a choice of dopamine agonists, MAO-B inhibitors or catechol-O-methyl transferase (COMT) inhibitors as an adjunct to levodopa for people with Parkinson's disease who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy, after discussing:*

  - *the person's individual clinical circumstances, for example, their Parkinson's disease symptoms, comorbidities and risks from polypharmacy*
  - *the person's individual lifestyle circumstances, preferences, needs and goals*
  - *the potential benefits and harms of the different drug classes*" [7]

  Currently where patients are intolerant or unresponsive to entacapone, the only available alternative COMT inhibitor across the local health economy is tolcapone. Use of tolcapone is undesirable for the reasons stated in point 1.

- Flexibility – The NICE evidence summary noted that for patients using differing levodopa doses at differing times of the day, it is not possible to use combination entacapone products. In such patients entacapone would need to be taken separately three times a day. The use of opicapone would reduce the tablet burden for these patients which could result in improved concordance and reduced swallowing difficulties. Opicapone may also be more appropriate in those patients who require modified release or dispersible levodopa who would otherwise have to take entacapone separately three times daily.
- Swallowing – Given that Parkinson's disease can cause swallowing difficulties and combination products containing entacapone tend to be the largest tablets available for the treatment of Parkinson's disease, opicapone may be a useful alternative option for those patients displaying difficulty swallowing the combination entacapone tablets.

References

[1] National Institute for Health and Care Excellence, "Parkinson's disease with end-of-dose motor fluctuations: opicapone," March 2017. [Online]. Available: https://www.nice.org.uk/advice/es9/chapter/Key-points. [Accessed 1 August 2018].

[2] Electronic Medicines Compendium, "Summary of Products Characteristics for Opicapone," Bial Pharma UK Ltd, 24 June 2016. [Online]. Available: https://www.medicines.org.uk/emc/product/7386. [Accessed 1 August 2018].

[3] Electronic Medicines Compendium, "Summary of Product Characteristics Tasmar 100mg tablets," Meda Pharmaceuticals, September 2014. [Online]. Available: https://www.medicines.org.uk/emc/product/3902. [Accessed 1 August 2018].

[4] European Medicines Agency, "Ongentys - European Public Assessment Report," 20 April 2016. [Online]. Available: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002790/WC500209538.pdf. [Accessed 1 August 2018].

[5] JJ Ferreira 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,* vol. 15, no. 2, pp. 154-165, 2016.

[6] JJ Ferreira et al, "Switching double-blind opicapone, entacapone or placebo to open-label opicapone: efficacy results from 1-year extension study BIPARKI," *Mov Disord,* vol. 31, p. (suppl 2): S633, 2016.

[7] National Institute of Health and Care Excellence, "Parkinson's disease in adults," July 2017. [Online]. Available: https://www.nice.org.uk/guidance/ng71/chapter/Recommendations. [Accessed 3 August 2018].

Appendix 1: Original New Medicine Review

Opicapone (Ongentys®▼) 50mg hard capsules. For 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 levodopa/DDCI inhibitors.

Summary of supporting evidence

- Study of primary endpoints of change in daily OFF time from baseline at 15 weeks met in 2 pivotal studies.
  - 60.8 minutes (CI95% 97.2; 24.4, p=0.001) in BIPARKI study.[10]
  - 54.31 minutes (CI95% 96.18; 12.44, adjusted p=0.0028) in BIPARKII study.[12]
- Secondary endpoints supporting primary endpoints and all with p values <0.05.
  - Proportion of OFF-time responders at the end of the blind phase vs placebo (69.6% vs 47.5 and 66.0% vs 50.4% in BIPARKI and BIPARKII respectively).
  - Proportion of ON-time responders at the end of the blind phase vs placebo (65.2% vs 45.8 and 61.9% vs 45.2% in BIPARKI and BIPARKII respectively).
- Safety and tolerability of opicapone is generally good and the majority of adverse events are comparable to other COMT inhibitors as stated by the EMEA.[11]
- Serious adverse events reported in 6% of patients in both studies with no single serious adverse events being reported in >1 patient.

Details of Review

Name of medicine (generic & brand name): Opicapone (Ongentys®)
Strengths and forms: 50mg Hard capsules[1]
Dose and administration: The recommended dose of opicapone is 50 mg as an adjunct to levodopa/DDCI inhibitors. Opicapone should be taken once-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.[1]
BNF therapeutic class / mode of action: Chapter 4.2 Parkinson's Disease, Catechol-o-methyltransferase inhibitors.

Opicapone is a peripheral, selective and reversible catechol-*O*-methyltransferase (COMT) inhibitor endowed with a high binding affinity (sub-picomolar) that translates into a slow complex dissociation rate constant and a long duration of action (>24 hours) *in vivo*.

In the presence of a DOPA decarboxylase inhibitor (DDCI), COMT becomes the major metabolising enzyme for levodopa, catalysing its conversion to 3-*O*-methyldopa (3-OMD) in the brain and periphery. In patients taking levodopa and a peripheral DDCI, opicapone increases levodopa plasma levels thereby improving the clinical response to levodopa.[2]

Licensed indication(s):

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]

Proposed use:

Within licensed indication

Course and cost:

30 x 50mg capsules cost £93.90; annual cost: £1142.45[2]

Current standard of care/comparator therapies:

COMT inhibitors: entacapone and tolcapone.

Relevant NICE guidance:

Not yet reviewed by NICE.

NICE CG35 (Parkinson's disease in over 20s: diagnosis and management) June 2006,[3] briefly indicates which drug classes should be used in late stage Parkinson's Disease (PD), indicating COMT inhibitors as potential first line choices in combination with co-beneldopa or co-careldopa.

1.5.1.1 It is not possible to identify a universal first-choice drug therapy for people with later PD.

The choice of adjuvant drug 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 drug classes.

Options for adjuvant pharmacotherapy in later PD

Adjuvant therapy for later PD	First-choice option	Symptom control	Risk of side effects	
			Motor complications	Other adverse events
Dopamine agonists	Yes	Moderate degree of symptom control	Evidence of reduced motor complications	Evidence of increased other adverse events
COMT inhibitors	Yes	Moderate degree of symptom control	Evidence of reduced motor complications	Evidence of increased other adverse events
MAO-B inhibitors	Yes	Moderate degree of symptom control	Evidence of reduced motor complications	Evidence of increased other adverse events
Amantadine	No	Non-significant result	Evidence of reduced motor complications	Evidence of increased other adverse events
Apomorphine	No	Limited degree of symptom control	Evidence of reduced motor complications	Evidence of increased other adverse events

In the NICE guideline, 'early disease' refers to PD in people who have developed functional disability and require symptomatic therapy. 'Later disease' refers to PD in people on levodopa who have developed motor complications. Opicapone is a peripheral, selective and reversible catechol-O-methyltransferase (COMT) inhibitor. Opicapone is only licensed as an adjunctive therapy in patients who cannot be stabilised on preparations of levodopa/DOPA decarboxylase inhibitors.

1.5.5.1 Catechol-O-methyl transferase (COMT) inhibitors may be used to reduce motor fluctuations in people with later PD.

1.5.5.2 In view of problems with reduced concordance, people with later PD taking entacapone should be offered a triple combination preparation of levodopa, carbidopa and entacapone.

1.5.5.3 Tolcapone should only be used after entacapone has failed in people with later PD due to lack of efficacy or side effects. Liver function tests are required every 2 weeks during the first year of therapy, and thereafter in accordance with the 'Summary of product characteristics'

Disease Background

Idiopathic Parkinson's disease (PD) is an adult-onset neurodegenerative disorder that is prevalent worldwide. Incidence increases sharply with age, with approximately 1 in 200 people over 70 years of age suffering from the disease.[4] PD is clinically characterised by resting tremor, bradykinesia, rigidity and gait disturbances. Progressive clinical impairment occurs, usually over a 10- to 15-year period, reflecting the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta, resulting in a significant loss of dopamine (DA) in the striatum.[5] DA replacement therapy remains the backbone of antiparkinson therapy.[6] As PD progresses, further symptoms appear that either do not respond to dopaminergic replacement therapy or are related to levodopa treatment. Disabling dyskinesias and motor fluctuations are often referred to as DA-related symptoms of PD, even though these complications are likely to be a consequence of underlying nigrostriatal degeneration, revealed by exposure to dopaminergic treatment.[5]

Current treatment options

Current symptomatic treatment relies on levodopa, DA agonists, monoamine oxidase B (MAO-B) inhibitors, and catechol- O -methyltransferase (COMT) inhibitors that compensate for the deficit in the nigrostriatal dopaminergic input pathways. The aim of COMT inhibitors is to reduce the metabolism of levodopa and thus increase the amount crossing into the brain, improving PD motor symptoms and reducing motor fluctuations in patients with later disease.[7] The SIGN guideline for PD reviewed the evidence base for COMT inhibitors, concluding that their use in patients with motor fluctuations resulted in statistically significant reductions of Unified Parkinson's Disease Rating Scale (UPDRS) total scores.[8] There is some evidence that peripheral COMT inhibition also delays onset of motor complications and supports occurrence of lower homocysteine plasma levels, which, when elevated, represent a risk factor for accelerated PD progression and arteriosclerosis.[5]

Tolcapone was the first COMT inhibitor to enter clinical practice in England and Wales but its European product licence was withdrawn in November 1998 after three cases of fatal hepatic toxicity. However, after further clinical experience in other markets and a forced switch from entacapone to tolcapone study, it was reintroduced in Europe. It is currently licensed, at a dose of 100 mg three times per day, for people who have failed on entacapone, and requires mandatory liver function test monitoring at 2-week intervals for the first year of treatment followed by less stringent monitoring ad infinitum.[7]

Entacapone is thought to be the best tolerated COMT inhibitor. It is used as an adjunct to each daily levodopa/DDCI dose, it extends the half-life of levodopa and this increases the bioavailability of the drug; consequently prolonging the effect of each levodopa dose. Unlike tolcapone which inhibits COMT centrally, entacapone has specifity for peripheral acting COMT producing a potent and reversible inhibition. [9]

Opicapone is the subject of this New Medicine Assessment. It is a novel, once-daily, potent third-generation catechol-O-methyltransferase inhibitor.[10] 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] Given the historical safety issues with the use of tolcapone, opicapone may be considered a safer alternative in patients who have not responded to treatment with an entacapone containing preparation.

Summary of efficacy data in proposed use:

Pivotal studies

Data from two pivotal 14-15 week, randomised, parallel double blind placebo-controlled studies were submitted to EMEA in support of opicapone's indication 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.[11] The studies included were **BIPARKI**[10] (n=600) and **BIPARKII**[12] (n=427). Both of these studies were continued as open label clinical trials for 12 months following completion of the blinded phases.

In the first of these studies **BIPARKI**, patients were randomised to receive either opicapone (doses 5mg, 25mg and 50mg), entacapone 200mg or placebo in additional to their current levodopa/DDCI combination medicine. The participants (aged 30–83 years) were eligible if they had a clinical diagnosis of Parkinson's disease for at least 3 years and at least 1 year of clinical improvement with levodopa treatment. Concomitant stable treatment for Parkinson's disease was allowed on the condition that the dose was kept stable. Patients who had previously used entacapone or were concomitantly using tolcapone and apomorphine were excluded from the study. In addition patients with clinically significant and unstable cardiovascular disease or

psychiatric illness (including major depression, dementia, impulse control disorders, and suicide ideation), or any other medical disorder that might have placed the patient at increased risk were also excluded. The primary endpoint was the change from baseline to the end of study treatment in absolute time in the "off" state, as assessed by daily paper patient diaries. Key secondary endpoints were the change from baseline to the end of study treatment in the proportion of patients (i.e., responders) achieving at least a 1-h reduction in absolute time in the off state and the change from baseline to the end of study treatment in the proportion of patients achieving at least a 1-h increase in absolute total time in the on state. [10]

In study **BIPARKII** the design of the trial mirrored the **BIPARKI** study with the exceptions of no active comparator (entacapone) being included or 5mg dose of opicapone. The primary objective in **BIPARKII** was to investigate the efficacy of two different doses (25 mg and 50 mg) of opicapone, administered once a day, compared with placebo, when administered with the existing treatment of L-DOPA plus a DDCI, in subjects with Parkinson's Disease and end-of-dose motor fluctuations. The secondary objective was to investigate the safety and tolerability of opicapone in comparison to placebo when administered with the existing treatment of L-DOPA/DDCI.

BIPARKI study results

In the **BIPARKI** study the change from baseline OFF-time (minutes) to endpoint (week 15) was 56 (CI95% 83.0; 29.4), 96.3 (CI95%117.5; 61.3) and 116.8 (CI95% 143.8; 87.5) minutes for placebo, entacapone 200mg and opicapone 50mg, respectively. Difference versus placebo for opicapone 50mg was 60.8 minutes (CI95% 97.2; 24.4, p=0.001). Where a non-inferiority margin of 30 minutes was set, tests proved that opicapone 50mg was non-inferior to entacapone 200mg (difference of 26.2 minutes, p<0.0167 threshold).

All secondary efficacy measures were consistent with the primary analysis. These included proportion of OFF-time and ON-time responders at endpoint. Compared to placebo (47.5%) the proportion of OFF-time responders was significantly higher (69.6%, p=0.0011), and likewise in ON-time responders versus placebo (65.2% vs 45.8%, p=0.0028).[10]

Study BIPARKII

In the **BIPARKII** study, change from baseline in absolute OFF-time to endpoint at week 15 was 64.46 minutes for placebo and 118.77 (95% CI 96.18; 12.44) minutes for opicapone 50mg producing a significant difference of 54.31 minutes (CI95% 96.18; 12.44, adjusted p=0.0081).

Secondary efficacy measured focussed on proportional OFF-time and ON-time responders at the end of the double blind period. Again secondary efficacy measures were consistent with primary measures analysis with 50.4% of placebo patients assessed as OFF-time responders compared with 66.0% of patients treated with opicapone 50mg. Similarly 45.2% of the placebo group were evaluated as ON-time responders compared with 61.9% in the group taking opicapone 50mg. The P-values for the differences were all <0.05 for the comparisons.[11]

Relevance of pivotal studies

The pivotal study **BIPARKI** shows that opicapone is effective in reducing OFF-time relative to the baseline compared to placebo**. BIPARKI** also demonstrated that opicapone was non-inferior to entacapone in terms of efficacy in reducing OFF-time. Study **BIPARKII** supports the **BIPARKI** study in proving clinical efficacy compared to placebo over 15 weeks.

Open label phase of the studies

Following completion of the blinded phase both trials continued with a 1 year open label part. The objective of Part II, the Open Label Extension Phase of the study, was to investigate the safety, tolerability and maintenance of therapeutic effect of opicapone (OPC) (25 mg OD or 50 mg OD) adjusted according to clinical response over 1 year of treatment, when administered with

the existing treatment of levodopa (L-DOPA) plus a DDCI, in Parkinson's disease (PD) patients with end-of-dose motor fluctuations who completed the Part I Double Blind Phase of the study. 367 subjects were enrolled into the open label part of the study.

Both studies supported the efficacy of opicapone 50mg, and improvements in symptoms were observed in all patient groups which had not commenced on opicapone 50mg at the start of the trial. The **BIPARKII** study reported mean changes in OFF-time relative to two baselines; baseline OFF-time at the start of the open label phase, and baseline OFF-time at the start of the double blind phase. In both cases at the end of the 1 year open label phase mean OFF-time reduction was reported (a change of 21.8 minutes from the open label baseline and 126.3 minutes from the double blind phase baseline). The OFF-time reduction was sustained over the open label period and even slightly improved compared to the end of the double-blinded period. This sustained OFF-time reduction was also demonstrated in the **BIPARKI** study further supporting the long term efficacy of opicapone.[11]

Summary of safety data:

In the completed studies, opicapone was administered at any dose (single or multiple) to a total of 1651 subjects: 859 healthy subjects and 792 subjects with Parkinson's disease. This includes 631 subjects with Parkinson's disease in the double blinded part of the Phase 3 studies taking up to 50 mg opicapone once daily for 14 to 15 weeks, plus a further 121 subjects newly exposed to opicapone (having received placebo in the double blinded part) in the 1-year open label extension of **BIPARKII** study. In addition, a further 99 subjects had been exposed to opicapone in the open-label part of the Phase 3 Study **BIPARKI**.[11]

The most frequently observed types of side effects for opicapone were in the nervous system (dyskinesia, headache, somnolence, dizziness, worsening of Parkinson's disease, and tremor), gastrointestinal system (nausea, upper abdominal pain, diarrhoea), skin and subcutaneous tissue disorders(hyperhidrosis and seborrheic dermatitis) and vascular system(hypertension).[11] Dyskinesia was the most common side effect occurring in 23.2% of patients in **BIPARKI.**[10]

Serious adverse events occurred in 6% of late stage PD patients in **BIPARKII** where no single serious adverse event was reported by more than 1 patient. In **BIPARKI** the incidence of serious adverse events was 6%. Although 15 deaths were reported during all the trials (including the 1 year open label extension), none could be directly attributed to opicapone.

The SPC for opicapone (Ongentys®) lists the following adverse events:[1]

Incidence of Event	Adverse Event
Very Common (≥1/10)	Dyskinesia
Common (≥1/100 to <1/10)	Abnormal dreams, hallucination, hallucination visual, insomnia dizziness, headache, somnolence, orthostatic hypotension, constipation, dry mouth, vomiting, muscle spasms, blood creatine phosphokinase increased
Uncommon (≥1/1,000 to <1/100)	Decreased appetite, hypertriglyceridaemia, anxiety, depression, hallucination auditory, nightmare, sleep disorder, dysgeusia, hyperkinesia, syncope, dry eye, ear congestion, palpitations, hypertension, hypotension, dyspnoea, abdominal distention, abdominal pain, abdominal pain upper, dyspepsia, muscle twitching, musculoskeletal stiffness, myalgia, pain in extremity, chromaturia, nocturia, weight decreased[1]

Opicapone is contraindicated in patients with tumours of the arenal glands including phaeochromocytoma, paraganglioma and other catecholamine secreting neoplasms. Patients

with a history of neuroleptic malignant syndrome and/or non-traumatic rhabdomyolysis should not use opicapone.[1]

The use of opicapone is contraindicated with monoamine oxidase inhibitors (MAOIs) except when these are used to treat Parkinson's disease.

Opicapone is to be administered as an adjunct to levodopa treatment thereby enhancing the effects of levodopa hence, the precautions valid for levodopa treatment should also be taken into account for opicapone. To reduce levodopa-related dopaminergic adverse reactions (e.g. dyskinesia, hallucinations, nausea, vomiting and orthostatic hypotension), it is often necessary to adjust the daily dose of levodopa by extending the dosing intervals and/or reducing the amount of levodopa per dose within the first days to first weeks after initiating treatment with opicapone, according to the clinical condition of the patient.[1]

The EMEA concluded in its public assessment report that Safety and tolerability of opicapone is generally good and the majority of adverse events are comparable to other COMT inhibitors.[11]

Strengths and limitations of the evidence:

Strengths:

- Opicapone has demonstrated a statistically significant effect, reducing OFF-time in patients with late stage PD in two large, placebo controlled trials.
- The **BIPARKI** study demonstrates non-inferiority of opicapone compared with entacapone in terms of both efficacy and safety.[10]
- Patients included in the 1 year open label extension study who had previously been treated with placebo (or lower opicapone doses) in the blind phase of the study exhibited the largest improvement in OFF-time symptoms when taking opicapone 50mg.
- The secondary endpoints across both studies supported opicapone's efficacy.
- The EMEA concluded that Safety and tolerability of Opicapone is generally good and the majority of adverse events are comparable to other COMT inhibitors.[11]

Limitations

- While in absolute terms the subjects who were on opicapone longer (those who received opicapone 50mg in the double blinded phase) exhibited larger overall improvement, the lack of control and limitations of the open label methodology preclude from making a reliable conclusion that there is an additional benefit in using opicapone early.[11]
- Excluded patients from the **BIPARKI** study included those who had previously been treated with entacapone and tolcapone. Given that these excluded patients may potentially have been treated with COMT inhibitors and not responded, this may introduce bias into this study.
- The exclusion of patients previously treated with COMT inhibitors in the **BIPARKI** study does not provide information to inform the practice of switching patients to opicapone from other COMT inhibitors. The **BIPARKI** study does not therefore demonstrate the use of opicapone as a second line treatment following unsuccessful treatment with other COMT inhibitors.
- Subjects with a lower BMI exhibited a greater tendency for adverse events although meaningful comparisons cannot be made from the limited data available.[11]
- Experience of use of opicapone in patients over 85 years of age is limited.[1]

Prescribing and risk management issues:

As there are no major safety concerns for opicapone, routine pharmacovigilance activities are sufficient to monitor the safety concerns of the product.[11] The Summary of product characteristics states that opicapone is contraindicated in patients with any catecholamine secreting neoplasms, history of neuroleptic malignant syndrome or non-traumatic rhabdomyolysis. As opicapone

inhibits the pathway responsible for catecholamine metabolism, patients using monoamine oxidase inhibitors other than for the treatment of Parkinsons's disease should not take opicapone. It should be noted that opicapone is a weak inhibitor of CYP2C8, therefore co-administration with repaglinide should be avoided.

Opicapone is a 'black triangle' medicine - the Commission on Human Medicines (CHM) and the MHRA encourages the reporting of all suspected adverse reactions (side effects) to newer drugs and vaccines, which are denoted by the Black Triangle symbol.[13]

During initiation and the early weeks of opicapone treatment it may be necessary to reduce the concomitant levodopa dosage to reduce the incidence or severity of adverse effects such as dyskinesia and hallucinations. Prescribers are advised to be vigilant for the signs and symptoms of impulse control disorders such as pathological gambling, binge eating or hypersexuality.[1]

Commissioning considerations:

Prescribing of COMT inhibitors across Lancashire October 2015 to September 2016

Drug	Items	Cost	Cost/item
Entacapone	1,362	£22,363	**£16.42**
Comtess® (entacapone)	35	£2,297	**£65.63**
Tasmar® (tolcapone)	7	£509	**£72.65**
Stalevo®, Stanek® and Sastravi® (entacapone combined with levodopa/DDCI)	(6,221)	(£319,816)	(£51.41)*
Entacapone element of Stalevo®, Stanek® and Sastravi® with cost of co-careldopa deducted	6,221	**£105,757**	**£17.00**
Prescribing data for Lancashire October 2015 to September 2016			

*The cost of entacapone when contained in a combined product (£17) is approximately equal to the cost of generic entacapone as a standalone product once the cost of co-careldopa (£27.83) has been deducted from the combined product.

Anticipated patient numbers and net budget impact

PD is a common neurological condition, estimated to affect 274 per 100,000 of the population.[14]

- Entacapone generic costs £5.80 for 30 tablets;
- Entacapone (Comtess®) costs of £16.38 for 30 tablets
- Tolcapone (Tasmar®) costs £95.20 for 100 tablets;
- The adjusted cost of entacapone in a combination product is £17 for 30 tablets.
- Opicapone costs £93.90 for 30 capsules

7625 items containing entacapone or tolcapone are prescribed each year in Lancashire. This is equivalent to 635 items per month therefore it can be estimated that there are 635 patients in Lancashire being treated with a COMT inhibitor.

£130,926 is spent on COMT inhibitors each year in Lancashire

If, in one year 10% of patients are prescribed opicapone instead of either entacapone (and Comtess®) or tolcapone:

- 10% of entacapone is 136 items.
- 10% of Comtess® is 4 items
- 10% of tolcapone is 1 item,
- 10% of entacapone when contained in combined product is 622 items.
- total 763 items which would cost **£71,111** if prescribed as opicapone.

A 10% reduction in entacapone, Comtess® and tolcapone would leave costs:

- £20,127 for entacapone
- £2068 for Comtess®
- £458 for tolcapone
- £95,181 for entacapone when contained in combined product
- Total new spend = **£117,834**

Calculated above, 10% of items as opicapone would cost £71,111 which is added to the entacapone and tolcapone figures giving a total cost for the year of £188,945

- The extra spend in one year because of the 10% uptake of opicapone will be £188,945 – £130,925 = **£58,019.**

Associated additional costs or available discounts:

None identified

Productivity, service delivery, implementation:

It is anticipated that patients with mid to late stage fluctuating PD would be under the ongoing care of a specialist.

Innovation, need, equity:

Opicapone offers once daily dosing to simplify a patient's dosage regimen while offering the potential benefit of reducing the total daily dose of levodopa required for motor control in late Parkinson's Disease. It must be noted however that entacapone combination products already exist therefore opicapone does not simplify dosage regimens in patient groups receiving these.

Opicapone may be preferable to tolcapone in patients who have discontinued entacapone and require a second line treatment. NICE recommends that tolcapone should only be used after entacapone has failed in people with later PD due to lack of efficacy or side effects. Liver function tests are required every 2 weeks during the first year of therapy, and thereafter in accordance with the 'Summary of product characteristics'.[3]

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: high quality randomised controlled trials (RCTs) with low risk of bias systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: clinical trials at moderate or high risk of bias systematic reviews or meta-analyses of such clinical trials or with inconsistent findings cohort studies case-control studies	
Level 3	Disease-oriented evidence, or evidence from: consensus guidelines expert opinion case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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