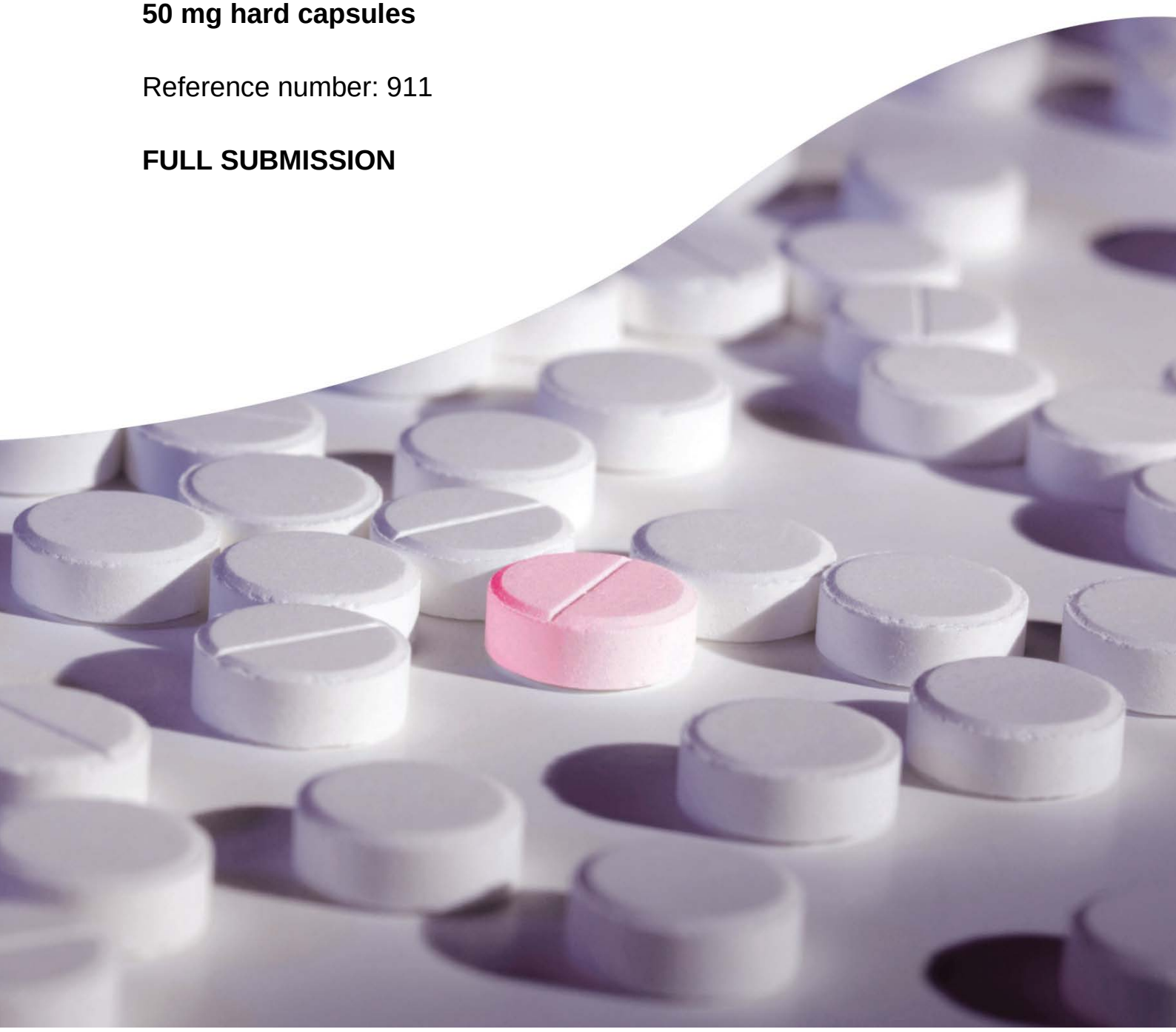
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Opicapone (Ongentys®)
50 mg hard capsules

Reference number: 911

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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AWMSG Secretariat Assessment Report
Opicapone (Ongentys®▼) 50 mg hard capsules

1.0 KEY FACTS

Assessment details	Opicapone (Ongentys®▼) for use as an adjunctive therapy to preparations of levodopa/DOPA decarboxylase inhibitors (DDCIs) in adult patients with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. The applicant company requests that AWMSG considers opicapone for use after failure of entacapone, or in patients who cannot tolerate entacapone or have concordance issues, in line with the One Wales interim commissioning decision (March 2019).
Current clinical practice	Levodopa in combination with DDCIs is the standard treatment for adults with Parkinson's disease. If dyskinesia or motor fluctuations develop despite optimal levodopa treatment, dopamine agonists, monoamine oxidase B (MAO-B) inhibitors or catechol-O-methyltransferase (COMT) inhibitors are given as oral adjunct therapies. Among the COMT inhibitors, entacapone is currently used as a first-line adjunctive treatment. Tolcapone (Tasmar®) is licensed for when other COMT inhibitors have failed or are not tolerated by patients. Opicapone is currently available through One Wales Interim Commissioning for people with Parkinson's disease after failure of entacapone or in patients who cannot tolerate entacapone or have concordance issues. This advice is interim to appraisal by AWMSG. The company states that opicapone represents an alternative COMT inhibitor for use after entacapone. The company submission includes tolcapone as the main comparator. Clinical experts in Wales state that tolcapone is rarely used due to an increased risk of hepatic toxicity. Clinical experts agree that there is an unmet need for a well-tolerated oral COMT inhibitor as a second line treatment option after entacapone.
Clinical effectiveness	The main evidence comes from two phase III double-blind studies (BIPARK I/II) and their respective open label extensions. BIPARK I compared opicapone with entacapone and placebo and BIPARK II compared opicapone and placebo. The double-blind phase of the studies showed that opicapone was superior to placebo and non-inferior to entacapone in

	reducing the time patients are in the OFF state. This reduction was maintained in open-label extension studies (one year of treatment in total). The prior treatment history of patients included in these studies does not fully align with the intended positioning of opicapone as second-line adjunctive therapy in Parkinson's disease in Wales. There are no direct comparative data of opicapone and tolcapone. No indirect comparative data was submitted by the company. Results from a real world study of opicapone in adults with Parkinson's disease (OPTIPARK) support the findings from the phase III BIPARK studies.
Cost-effectiveness	A cost-utility analysis compares opicapone with tolcapone as a second-line COMT inhibitor adjunctive to preparations of levodopa/DDCI in adult patients with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations. The company base case suggests that opicapone is [commercial in confidence figure removed] less costly and produces an additional 0.07 quality-adjusted life-years (QALYs) over the 25-year time horizon, thus dominating tolcapone. The model structure is robust to sensitivity and scenario analyses provided by the company, with estimates for opicapone dominant in all scenario analyses. However, the cost-utility analyses are subject to considerable uncertainty due to the paucity of high-quality available data.
Budget impact	The company estimates that 137 patients would receive treatment with opicapone in Wales in Year 1, increasing to 751 in Year 5. The company base case suggests that introducing opicapone would lead to a net acquisition cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. The base case also predicts NHS resource savings valued at [commercial in confidence figure removed] in year 1, decreasing to [commercial in confidence figure removed] in year 5. These result from reduced cost of liver monitoring required for tolcapone. Basic sensitivity analysis showed that the budget impact was sensitive to changes in opicapone uptake and tolcapone discontinuation rates with budget impact estimates between [commercial in confidence figure removed] and [commercial in confidence figure removed] in Year 1, increasing to between [commercial in confidence figure removed] and [commercial in confidence figure removed] in Year 5.

	The budget impact analysis is subject to considerable uncertainty based around the eligible population for opicapone and rates of use of tolcapone.

This assessment report is based on evidence submitted by BIAL Pharma UK Ltd[1] and an evidence search conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) on 22nd October 2020.

2.0 BACKGROUND

2.1 Condition and clinical practice

Parkinson's disease is a progressive neurodegenerative condition resulting from the death of dopamine-containing cells in the substantia nigra of the brain[2]. Parkinson's disease usually presents later in life, with a mean age of onset of about 60 years[3]. There is currently no cure for Parkinson's disease. Treatments aim to manage the symptoms which include bradykinesia (slow movements), rigidity, rest tremor (shaking) and postural instability (loss of balance). Alongside physical symptoms, people with Parkinson's can also suffer from depression, hallucinations, and dementia[2]. An inability to control these symptoms significantly impacts on a person's quality of life[4].

Levodopa is the most effective treatment of Parkinson's disease[5]. Progression of the disease and/or the requirement for long-term use of levodopa will lead to the development of motor complications such as motor fluctuations and dyskinesias[6]. These cause large variations in motor performance to occur, with normal function during 'ON' periods and weakness and restricted mobility during 'OFF' periods. Oral adjunct therapies are predominantly used to treat dyskinesias / motor fluctuations, these include dopamine agonists, monoamine oxidase type B (MAO-B) inhibitors and catechol-O-methyltransferase (COMT) inhibitors, before more invasive approaches are necessary[6].

COMT inhibitors are an established part of the Parkinson's disease pathway in Wales. Among the COMT inhibitors, entacapone is currently used as a first-line adjunctive treatment. Entacapone (Comtess®) has low to moderate oral bioavailability which requires frequent dosing[7]. Tolcapone (Tasmar®) is a more potent inhibitor of COMT than entacapone however, due to an increased risk of hepatic toxicity, its use is limited to fluctuating patients who have failed or are intolerant to other COMT inhibitors[8,9]. Opicapone (Ongentys®) is currently available through One Wales Interim Commissioning for people with Parkinson's disease after failure of entacapone, or in patients who cannot tolerate entecapone or have concordance issues. This recommendation is interim to appraisal by AWMSG. Treatments for advanced Parkinson's disease are invasive and resource-intensive, suggesting there may be a place for alternative oral therapies which delay the transition to these later therapies.

2.2 Medicine

Opicapone is a peripheral, selective and reversible COMT inhibitor[3]. In the presence of a DOPA decarboxylase inhibitor COMT becomes the major metabolising enzyme, and a considerable amount of levodopa is metabolised to 3-O-methyl-levodopa in the brain and periphery[3]. COMT inhibitors increase the plasma levels of levodopa when used with a DOPA decarboxylase inhibitor, thereby increasing the clinical response to levodopa[3,10].

The recommended dose of opicapone is a 50 mg tablet taken once daily[10]. Opicapone should be taken at bedtime at least one hour before or after levodopa combinations. Dose adjustments to levodopa therapy within the first days to first weeks after starting treatment with opicapone are often necessary to reduce levodopa-related dopaminergic reactions (e.g. dyskinesia, nausea, vomiting and orthostatic hypotension)[10].

The company have requested that the All Wales Medicines Strategy Group (AWMSG) consider opicapone for use after failure of entacapone or in patients who cannot tolerate entacapone or have concordance issues in line with the One Wales interim commissioning decision.

Opicapone was licensed in June 2016 and recommended for use in Wales through the One Wales Interim Commissioning process in March 2019. This positive interim recommendation allowed the company the opportunity to review the results of a phase IV open-label study (OPTIPARK, see section 3.4) and provide Welsh patients access to opicapone, whilst giving the company a chance to collect outcome data to support their submission to AWMSG.

2.3 Comparators
The company submission includes tolcapone as the comparator.

2.4 Guidance and related advice
- NICE quality standard (QS164; 2018) Parkinson's disease[11]
- NICE guideline (NG71; 2017) Parkinson's disease in adults[2]
- NICE evidence summary (ES9; 2017) Parkinson's disease with end-of-dose motor fluctuations: opicapone[6]

One Wales Interim Commissioning Decision, Opicapone (Ongentys®) as an adjunctive therapy to preparations of levodopa/DOPA decarboxylase inhibitors in adult patients with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations, February 2019[12].

2.5 Prescribing and supply
AWTTC is of the opinion that, if recommended, opicapone (Ongentys®) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

3.0 CLINICAL EFFECTIVENESS

The company's submission includes evidence from two phase III, double-blind, randomised controlled studies (BIPARK I & BIPARK II) and their respective open label extension studies, as summarised below. Also discussed in this section is a prospective observational study (OPTIPARK), which forms the evidence base for the real world use of opicapone.

3.1 BIPARK I
BIPARK I was a phase III randomised, active and placebo-controlled, double-blind 14-15 week, multicentre (not including the UK) study to assess the safety and efficacy of opicapone compared with entacapone and placebo in adults diagnosed with mild to mid-stage idiopathic Parkinson's disease (Hoehn-Yahr stage of 1–3) [during the on state]), with end-of-dose motor fluctuations[13]. Patients were on a stable dose of

levodopa (three to eight daily doses) and other medicines for Parkinson's disease (mainly dopamine agonists). Patients had to have signs of end-of-dose motor fluctuations for at least four weeks before screening, with a mean total awake time in the OFF state of at least 1.5 hours, excluding morning akinesia. Patients experiencing severe and/or unpredictable OFF periods (when patients are symptomatic) were excluded. Concurrent anti-Parkinsonian medicines were allowed with the exception of tolcapone, apomorphine (withdrawn ≥1 month before screening), and entacapone (other than that supplied for the study)[13].

For the double-blind study patients were randomised (1:1:1:1:1) to receive oral opicapone (5 mg, 25 mg or 50 mg), placebo, or entacapone (200 mg with every levodopa intake) for 14–15 weeks[13]. After completing the double-blind period, patients could enter an additional 52-week, open-label extension period in which all patients received opicapone treatment[14]. Only data for the licensed (50 mg) dose of opicapone are presented below.

The primary endpoint was the change in absolute time in the OFF state from baseline to the end of the double-blind phase, assessed by daily patient diaries[13]. All analyses were based on the full analysis set (FAS) with the exception of non-inferiority to entacapone which was done using the per protocol set (PPS). The FAS consisted of all randomized patients who took at least 1 dose of study medication and had at least 1 post baseline off-time assessment The adjusted least-squares mean change from baseline in absolute time in the OFF state was –116·8 min in the opicapone 50 mg group, compared with –96·3 min in the entacapone group, and –56·0 min in the placebo group (Table 1). Opicapone 50 mg was superior to placebo and non-inferior to entacapone (Table 1)[13].

Table 1. Primary endpoint results from the BIPARK I study[13]

	Placebo (n=120)	Entacapone (n=120)	Opicapone 50 mg (n=115)
Change in absolute time in the OFF state from baseline*			
Least-squares mean change (minutes)	−56.0	−96.3	−116.8
95% CI	−82.3 to −29.7	−122.6 to −70.0	−144.2 to −89.4
Change in absolute time in the OFF state compared with placebo*			
Mean difference (minutes)	-	−40.3	−60.8
95% CI	-	−76.2 to −4.3	−97.2 to −24.4
p value	-	0.014	0.0015
Change in absolute time in the OFF state compared with entacapone†			
Mean difference (minutes)	-	-	−26.2
95% CI	-	-	−63.8 to 11.4
p value	-	-	0.0051
CI: confidence interval. * Full analysis set, n = 590 † Per protocol set, n = 537			

A key secondary efficacy endpoint was ON time (when patients' symptoms are controlled) without troublesome dyskinesia. This was significantly increased in the opicapone 50 mg group by 62.6 minutes compared with placebo (95% confidence interval: 23.8–101.4; P=0.002)[13]. Other secondary endpoints including the number of patients reporting ≥ 1 hour in time in the OFF state at the end of treatment, number reporting ≥ 1 hour in time in the ON state at the end of treatment, and the total time in the ON state at end of study treatment also showed a statistically significant improvement with opicapone 50 mg when compared to placebo. A statistically significantly higher proportion of patients in the opicapone 50 mg group showed improvements from baseline in Clinician's and Patient's Global Impression of Change scores compared with patients in the placebo and entacapone groups. A numerical improvement in quality of life score (39 item Parkinson's disease questionnaire; PDQ-39) and sleep (Parkinson's disease sleep scale; PDSS) was observed however the differences between active treatment (opicapone and entacapone) and placebo were not statistically significant[13].

Long term safety and efficacy was assessed in a 52–week, open-label extension study, which enrolled 495 people (432 completed the open label phase)[14]. The participants started open-label treatment with 25 mg opicapone, which could be titrated up to 50 mg if greater symptom control was needed (210 [42%] patients increased their opicapone dose to 50 mg during the open label phase). The median reductions in OFF time were 33.8 minutes compared with the open-label baseline, and 126.9 minutes compared with the double-blind baseline. Decreases in OFF time were associated with increases in absolute ON time without dyskinesia, but no relevant changes were observed in the median ON times with troublesome or non-troublesome dyskinesia during the open-label phase. Patients who received opicapone 50 mg in the double-blind phase maintained their efficacy. Switching treatments from placebo and entacapone led to further significant decreases in OFF time (−64.9 and −39.3 minutes respectively), and increases in ON time (66.9 and 30.1 minutes) and ON time without dyskinesia (43.1 and 45.7 minutes) from open label baseline to visit 14 (study end)[14].

3.2 BIPARK II

BIPARK II was a phase III randomised, placebo-controlled, double-blind 14-15 week, multicentre (including the UK) study to assess the safety and efficacy of opicapone compared with placebo in adults diagnosed with Parkinson's disease with end-of-dose motor fluctuations[15]. The inclusion and exclusion criteria for BIPARK II was the same as BIPARK I (see section 3.1).

For the double-blind period of the study patients were randomised (1:1:1) to receive opicapone (25 mg or 50 mg) or placebo for 14–15 weeks[15]. A day after completing the end of the double-blind period, patients entered the 1-year open label phase and received opicapone treatment. Only data for the licensed (50 mg) dose of opicapone are presented below.

The primary endpoint was the change in absolute time in the OFF state from baseline to the end of the double-blind phase, assessed by daily patient diaries[15]. The mean change from baseline in absolute time in the OFF state was larger in the opicapone 50 mg group at −118.8 minutes, compared with −64.5 minutes in the placebo group (Table 2). The adjusted treatment difference for opicapone 50 mg compared with the placebo group was significant (P=0.008) (Table 2)[15].

Table 2. Primary endpoint results from the BIPARK II study[15]

	Placebo (n=135)	Opicapone 50 mg (n=147)
Change in absolute time in the OFF state from baseline*		
Least-squares mean change in minutes (SD)	−64.5 (14.4)	−118.8 (13.8)
Difference in least-squares mean (SE) compared with placebo (minutes)	-	−54.3 (18.9)
95% CI for difference with placebo	-	−96.2 to −12.4
p value	-	0.008
CI: confidence interval; SD: standard deviation; SE: standard error. *Full analysis set, n = 407		

A key secondary efficacy endpoint was ON time without troublesome dyskinesia. This was increased in the opicapone 50 mg group by [commercial in confidence figure removed] compared with placebo however this difference was not significant[1]. Other secondary endpoints including the number of patients reporting ≥ 1 hour in time in the OFF state at the end of treatment, number reporting ≥ 1 hour in time in the ON state at the end of treatment, and the total time in the ON state at end of study treatment showed a statistically significant improvement with opicapone 50 mg when compared to placebo[15]. No differences between opicapone 50 mg and placebo were found for Clinician's and Patient's Global Impression of Change, PDSS nor the PDQ-39 [15].

Long term efficacy was assessed in a 52–week, open-label extension study, which enrolled 367 people from the double-blind study, including two patients who had discontinued the double-blind phase early owing to lack of study medication (286 completed the open label phase)[15]. The participants started open-label treatment with 25 mg opicapone, which could be titrated up to 50 mg if greater symptom control was needed. The adjusted mean reduction in OFF time from the start to the end of this phase was 18.31 minutes. Mean total ON time increased by 24.9 (standard deviation 156.4) minutes and the mean ON time with troublesome dyskinesia increased by 6.0 (standard deviation 129.1) minutes[15].

3.3 Pooled Analysis of BIPARK I and BIPARK II

Pooled analysis of BIPARK I and BIPARK II was done based on integration of individual participant data. Analyses of the double-blind and open label phases included data from all patients randomised to placebo or opicapone 50 mg (common treatment arms in both studies) in the double-blind phase, who took one or more doses of study medication and had one or more post-baseline OFF time assessments (FAS population)[16]. The pooled results confirm the findings from the individual trials reported in sections 3.1 and 3.2 and are therefore not repeated here.

3.4 OPTIPARK (NCT02847442)

OPTIPARK was a phase 4, multicentre, prospective, open-label, single-arm trial conducted in Germany and the UK [commercial in confidence text removed] under clinical practice conditions[17]. Adults with idiopathic Parkinson's disease (Hoehn and Yahr stages 1–4 [during ON state] and motor fluctuations (at least one symptom on the 9-Symptom Wearing-off Questionnaire [WOQ-9]) were treated with opicapone 50 mg for 3 (Germany) or 6 (UK) months in addition to their current levodopa and other antiparkinsonian treatments[17]. Patients previously or currently treated with tolcapone and/or opicapone were excluded from the study.

The primary outcome was the Clinician's Global Impression of Change score after 3 months of treatment with opicapone 50 mg[17]. A total of 506 patients were enrolled and 477 were included in the full analysis set. After 3 months of treatment with opicapone 50 mg, the majority of patients (71.3%) showed clinical improvement as judged by the investigators, with 43% reported as much or very much improved. For those UK

patients (n = 95) who were also assessed at 6 months, 85.3% were judged as improved since commencing treatment (8.5% very much improved and 49.4% much improved) while 8.5% were judged as showing 'no change' and 6.6% as having worsened[17].

Improvements were also found for a number of secondary analyses [17]. These included the unified Parkinson's disease rating scale (UPDRS), 8-item Parkinson's disease questionnaire (PDQ-8) and the non-motor symptom scale (NMSS). After three months opicapone 50 mg once daily was associated with statistically significant improvements in UPDRS activities of daily living (Part II) during OFF time (−3.0 ± 4.6 p<0.0001), UPDRS motor scores (Part III) during ON time (-4.6 ± 8.1, p<0.0001) and total scores (Parts II + III) during ON time (-6.4 ± 10.4, p<0.0001)[17]. The observed change in UPDRS motor score represents a moderate clinically important difference[18]. The change in UPDRS total score represents a minimal clinically important difference[18]. Significant improvements after three months were also observed in both patient quality of life (PDQ-8; -3.4 ± 12.8, p<0.0001) and non-motor symptoms (NMSS; -6.8 ± 19.7, p<0.0001)[17].

3.4 Comparative safety

The summary of product characteristics (SPC) lists adverse events associated with opicapone[10]. The most common of which is dyskinesia. Other events include, but are not limited to, vascular disorders (hypotension and hypertension), psychiatric disorders (such as hallucinations, anxiety and depression) and gastrointestinal disorders. 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[10].

In the double-blind phase of the BIPARK studies, the incidence of serious treatment-emergent adverse events in both studies was low across all groups (≤ 7%)[13,15]. The most common adverse events occurring in the opicapone group compared with the placebo group were dopaminergic in nature (dyskinesia, constipation, insomnia and dry mouth). Dyskinesia was the most commonly reported treatment emergent adverse event, with most of the dyskinesia events occurring in patients who were already experiencing dyskinesia at baseline. Clinical effectiveness data suggests that most dyskinesias were not considered troublesome by the patients[13,15].

The long-term safety (up to 1 year) in the extension studies is in line with the known post-marketing safety profile of opicapone and the findings from the double-blind studies. Dyskinesia was the most commonly reported treatment emergent adverse event (≤ 21.5% in both studies)[14,15]. In general, most treatment-emergent adverse events were mild or moderate in severity, transient and manageable by adjusting the levodopa or opicapone dose. This was supported by the low discontinuation rates[19].

Safety data reported in the OPTIPARK study was in line with the BIPARK studies with the most frequent treatment-emergent adverse events considered possibly treatment-related being dyskinesia, dry mouth and dizziness[17].

The Committee for Human Medicinal Products (CHMP) concluded that the safety and tolerability of opicapone is generally good and the majority of adverse events are comparable to other COMT inhibitors[3].

3.5 Ongoing studies

Three clinical trials with opicapone are currently being conducted. An observational study (NCT03959540) is evaluating the safety and efficacy of starting opicapone in

elderly patients with Parkinson's disease and is expected to complete data collection in 2020. The OpiSleep trial is assessing the effects of opicapone in patients with Parkinson's disease and sleep disturbances and the opicapone effect on patients with motor fluctuations and pain (OCEAN) study is evaluating the effects of opicapone on Parkinson's disease-associated pain.

3.6 AWTTC critique

- The company submission focuses on a subpopulation of the licensed indication in line with One Wales Interim Commissioning Decision, for use in patients where entacapone has failed or where entacapone is not tolerated, or is associated with concordance issues. Clinicians in Wales support the positioning of opicapone as a second-line COMT inhibitor and have indicated there is an unmet need for use in patients after entacapone.
- The treatment history of patients included in the clinical trial programme does not fully align with the intended positioning of opicapone as second-line adjunctive therapy in Parkinson's disease in Wales. In BIPARK I patients who had previously taken entacapone were excluded. In the open-label extension phase of BIPARK I, patients were switched from entacapone to opicapone and followed through one year. BIPARK II and OPTIPARK had a small percentage of entacapone/tolcapone-experienced patients ([commercial in confidence figure removed])[1] who switched to opicapone. However, there is no indication as to whether these patients were not responding to or tolerating entacapone.
- The BIPARK I study did not include centres in the UK; participants may not reflect the UK population and routine clinical practice.
- Analysis of BIPARK studies was based on the full analysis set (590/600 in BIPARK I[13] and 407/427 in BIPARK II[15]). The SPC[10] and European public assessment report[3] presented the intention-to-treat analysis and therefore the results differ to those reported in peer review publications and this submission. Although the numbers are different the conclusions remain the same.
- There are three COMT inhibitors marketed in the UK: entacapone, tolcapone and opicapone. Tolcapone is licensed for Parkinson's disease and motor fluctuations in patients who have failed to respond or are intolerant of other COMT inhibitors. The company have therefore chosen tolcapone as the most appropriate comparator for use after entacapone.
- Unlike entacapone and opicapone, tolcapone has an increased risk of hepatic toxicity and requires regular liver function tests. Clinical expert opinion suggests that due to the risk of hepatic toxicity, which requires additional monitoring and blood tests, many patients prefer not to receive tolcapone or will often not be suitable for tolcapone. Prescribing data indicates that tolcapone is rarely used in Wales.
- Diarrhoea has been considered a common adverse event for COMT inhibitors however gastrointestinal rates, including diarrhoea, were <2% in the BIPARK studies[19] and <1% in OPTIPARK[17].
- No studies have been conducted that directly compare opicapone and tolcapone. Comparisons of opicapone versus entacapone[13] and tolcapone versus entacapone[20] are available, as well as opicapone versus placebo[13,15] and tolcapone versus placebo[21] but no indirect comparative data was submitted by the company. The company suggest that this is because they didn't have access to patient-level data from these studies.
- Opicapone is given as a once daily dose, which offers a simplified regimen compared to entacapone and tolcapone. Using once-daily opicapone enables flexible dosing of levodopa at different times of the day without altering the opicapone dose.

4.0 COST-EFFECTIVENESS

4.1 Context

The company submission includes a cost-utility analysis (CUA) comparing opicapone (50 mg once daily) with tolcapone (100 mg three times daily) as second-line 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].

The CUA takes the form of a Markov model, with a 25-year time horizon and an NHS Wales/Personal and Social Services perspective. Costs and outcomes are discounted at a rate of 3.5% where the time horizon exceeds one year. The model was adapted from previously published models[22-24] and comprises three health states: <25% OFF time, >25% OFF time and death. OFF time is thereby defined as the proportion of the day that a patient spends awake and in the OFF time state. Patients enter the model in either the <25% OFF time health state (10% of patients) or the >25% OFF time (90% of patients) health state, with the initial distribution of patients between these health states based on baseline data from the BIPARK I trial[13]. Patients are assumed to start treatment with opicapone or tolcapone, respectively at model entry. The first model cycle spans three months, after which patients move between health states (including moving from >25% OFF time to <25% OFF time). Transitions are based on transition probabilities randomly sampled from gamma distributions to which the three-month outcome data from the BIPARK studies[13,15] for opicapone and published data for tolcapone[25] was fitted. All subsequent cycles are assumed to be 1 year long and patients can only remain stable or decline (i.e. transitions from the >25% OFF time to <25% OFF time state are no longer possible) based on natural rate of disease progression[23].

The model takes into account adverse events including dyskinesia, insomnia, constipation, diarrhoea, nausea and hallucinations. Probabilities of adverse events were based on the pivotal trials for opicapone[13,15] and published evidence for tolcapone[25]. Based on the mean baseline patient age in the BIPARK I trial[13], all patients are assumed to enter the model at a mean age of 64 years. Mortality is based on age- and gender-specific mortality rates obtained from UK national life tables, adjusted for Parkinson's disease with a hazard ratio of 1.61[26]. The model assumes that treatment choice has no impact on mortality.

Due to the lack of available data, treatment discontinuation rate was estimated by two Welsh clinicians[27]. Discontinuation rates for opicapone were considered to follow a similar pattern to entacapone, but assumed to be slightly lower (due to the slightly lower incidence of diarrhoea) and to only occur in the first three model cycles. Tolcapone discontinuation rates are based on estimates from a Delphi panel questionnaire completed by a number of European consultants, of which 5 where UK-based clinicians, to inform the global model (no reference available). It is assumed that, after discontinuation, any therapeutic benefit from treatment is lost and OFF time increases without further improvement possible.

Daily doses of opicapone, tolcapone and levodopa were taken from the pivotal trial[13] and published literature[25] and costed using standard unit costs[28]. Healthcare resource use associated with adverse events was estimated by two Welsh clinicians[27]. Other healthcare resource use, including hospital admissions, specialist and Parkinson's disease nurse visits and GP visits, was obtained from an observational study evaluating the cost burden of Parkinson's disease [29] and converted to apply to the two

OFF time health state of the models. Standard unit costs were applied[28,30,31]. The model also takes into account the cost of liver monitoring required for patients in the tolcapone group following a pathway advised by clinical experts[27] and monitoring recommendations[28]; costs were taken from published sources[30,32].

No utility data were collected in the pivotal studies[13,15]. Utilities were therefore taken from a US study which used visual analogue scale and standard gamble approaches to derive utility estimates from 60 Parkinson's disease patients for five distinct OFF time per day states[33]. These five states were combined and averaged to fit the model. No disutilities were applied for adverse events.

Deterministic and probabilistic sensitivity analyses were conducted to test the influence of the uncertainty of individual parameters on the model results. Scenario analysis explored the effect of treatment effectiveness in Cycle two and discontinuation rates on the results.

4.2 Results

The results of the base case are detailed in Table 3. When compared with tolcapone, opicapone is [commercial in confidence figure removed] less costly and produces an additional 0.07 quality-adjusted life-years (QALYs) over the 25-year time horizon. The higher cost for tolcapone is predominantly driven by the liver monitoring requirement, higher costs for adverse event treatment and more patients remaining in the >25% OFF time state after the first cycle where healthcare resource use (including hospitalisation probability, length of stay and GP and specialist visits) is higher. The slightly higher number of QALYs is caused by the higher likelihood of opicapone patients to move to the <25% OFF time state after the initial three-month cycle.

Table 3. Results of the base case analysis

	Opicapone	Tolcapone	Difference
Medicine acquisition costs*	¶¶	£13,869	¶¶
Administration costs	£0	£0	£0
Healthcare costs (including hospitalisations, specialist, GP and PD nurse visits)	¶¶	£712,486	¶¶
Total costs	¶¶	£730,844	¶¶
Total QALYs	7.77	7.70	0.07
ICER (£/QALY gained)	**Opicapone dominates**		

*Acquisition costs include costs of opicapone and tolcapone, respectively as well as levodopa cost and cost of liver monitoring for tolcapone.
¶¶ commercial in confidence figure removed.
PD: Parkinson's disease; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

The company performed a deterministic sensitivity analysis, but disaggregated incremental results were not provided. Instead the net monetary benefit (NMB) approach was followed on the basis that in the base case analysis, opicapone dominated tolcapone. The results indicated that in the performed sensitivity analysis the NMB remained positive. The OFF time improvement in cycle 1, hospital admission and length of stay and natural rate of disease progression impacted most on cost-effectiveness results.

Probabilistic sensitivity analyses indicate that opicapone has a 99% probability of being cost-effective at both willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained.

The results of the scenario analyses are assessed in order of plausibility in Table 4.

Table 4. Results of scenario analyses

Scenarios	ICER	Plausibility
20% improvement in effectiveness after first cycle for both treatment options assumed	**Opicapone dominates**	The plausibility of this scenario is uncertain as it is unclear upon what evidence the change was based.
20% decrease in effectiveness assumed after first cycle for both treatment options	**Opicapone dominates**	The plausibility of this scenario is uncertain as it is unclear upon what evidence the change was based.
20% improvement in effectiveness assumed after first cycle for opicapone only	**Opicapone dominates**	The plausibility of this scenario is uncertain as it is unclear upon what evidence the change was based.
20% improvement in effectiveness assumed after first cycle for tolcapone only	**Opicapone dominates**	The plausibility of this scenario is uncertain as it is unclear upon what evidence the change was based.
Cumulative 5% discontinuation rate per cycle starting at 15% assumed for opicapone	**Opicapone dominates**	The plausibility of this scenario is uncertain as it is unclear upon what evidence the change was based.
Cumulative 5% discontinuation rate per cycle starting at 5% assumed for opicapone	**Opicapone dominates**	The scenario has some plausibility as it is supported by the experience of two Welsh clinical experts for the first three cycles. It is assumed that the discontinuation rate continues to increase at a similar rate beyond this point.
Same discontinuation rate for opicapone as for tolcapone	**Opicapone dominates**	This scenario is less plausible than the base case as it is unlikely that discontinuation rates would be same considering the less favourable safety and adverse event profile of tolcapone.

4.3 AWTTC critique

The submission is characterised by both strengths and limitations:

Strengths:

- The submission gives a transparent account of the methods and data sources used in the analysis.
- Reasonable justifications are provided for the assumptions applied in the model and the model is well presented and appears robust and well-structured.
- The company has made an effort to use the best available data.

Limitations:

- The company submission positions opicapone as a second-line adjunctive treatment after entacapone and the cost-utility analysis presented by the company compares opicapone to tolcapone, both as second-line treatments. Clinical expert opinion and prescribing data indicate that due to an increased risk of hepatic toxicity and the additional monitoring requirements there is very little use of tolcapone in Wales. The cost-utility analysis may therefore not reflect the intended use of opicapone in Wales. The company states that modelling opicapone against best supportive care would have been too complex and would risk not being representative of a majority of patients.
- A considerable limitation of the CUA is the lack of high-quality, relevant, up-to-date data available to populate the model. A lot of the data informing the model is dated and not UK-specific which will introduce bias of unknown proportions.
- Efficacy measurements which inform the QALY differences between the opicapone and tolcapone arms are entirely driven by differences in OFF time improvement after the first three months of treatment whereby opicapone has a slightly higher probability of achieving transitioning from the >25% OFF time to the <25% OFF time health states than tolcapone. These transition probabilities are modelled using a basic naïve indirect comparison. The company suggests that a formal indirect treatment comparison was not possible due to a lack of patient-level data from tolcapone trials and that pooling analyses through meta-analyses or network meta-analyses was considered unfeasible due to the lack of available data. However, the use of a naïve indirect comparison, combined with heterogeneity in trial design, methods and populations, will introduce considerable bias and uncertainty into the results.
- Furthermore, the transition probabilities for tolcapone are based on dated and limited evidence[25], necessitating the use of numerous assumptions and considerable data manipulation in order to inform the model.
- Disease progression from cycle two of the model onwards is based on values used in the model published by Nuijten et al. (2001)[23]. These values were taken from Beck et al. (1982)[34] who undertook an approximation of life expectancy estimates for different diseases. It is unclear how much uncertainty is introduced by using very dated approximations to model disease progression in the current model.
- Daily doses of tolcapone and levodopa taken together with tolcapone are based on data collected pre-1997 in the USA and Canada[25]. It is unknown how applicable these dosing data are to the current Welsh context.
- The cut-off point for differentiation of health states in the Markov model of 25% was taken from a study that suggested lower quality of life and higher costs for patients with less than 25% OFF time[35]. However, these data are based on 40 outpatients with Parkinson's disease in Germany in 1995 and may not be generalisable to the 2020 Welsh population.

- A number of model inputs including discontinuation rates and healthcare resource use were based on key-opinion leaders input rather than published evidence.
- The company did not provide recalculated ICERs as part of the deterministic sensitivity analysis but reported NMB instead. The cost-effectiveness threshold for the NMB calculation was not reported but appears to be based on £30,000 per QALY. A £20,000 threshold would have been a more appropriate measure in this instance.

4.4 Review of published evidence on cost-effectiveness

A literature review conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) did not identify any studies relevant to the cost-effectiveness of opicapone versus tolcapone as second-line adjunctive therapy to preparations of levodopa/ DDCI in adult patients with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations.

5.0 BUDGET IMPACT

5.1 Context and methods

The company estimates an annual prevalence of Parkinson's disease in Wales of 11,667 patients, with an annual incidence of 2,145 new patients per year. These estimates are based on a prevalence rate of 370 per 100,000 people and an incidence rate of 68 per 100,000[36] applied to the Welsh population[37]. This results in a total number of 13,812 patients per year which is kept constant over the 5-year time horizon of the analysis. Mortality is not included separately as the company states that the incidence and prevalence rate obtained from Orayj et al. (2019) already accounts for mortality[36]. Based on recent prescribing data for Wales[31], the company assumes that, of these patients, 12,020 will receive levodopa. According to clinical experts[27], 25% of patients using levodopa will experience end-of-dose motor fluctuations, equating to 3,005 patients in Wales eligible for treatment with opicapone every year if first-line entacapone treatment fails, or a patient has significant concordance issues, swallowing difficulties or extreme levodopa dose fractionation. The company estimates an uptake rate of 5% in Year 1, increasing to 25% in Year 5, which results in 150 patients receiving opicapone in Year 1, increasing to 751 in Year 5. Taking into account treatment discontinuations taken from the cost-effectiveness model, this results in 137 patients receiving opicapone in Year 1, 259 in Year 2, with no further discontinuation assumed after Year 3. Annual costs of [commercial in confidence figure removed] were applied for opicapone and £1,047 for tolcapone.

The company provided basic sensitivity analysis changing all parameter values by ±5% and altering opicapone uptake and tolcapone discontinuation rates.

5.2 Results

The budget impact is presented in Table 5. The company estimates that introducing opicapone would lead to a net acquisition cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5 with an overall budget impact over the 5-year period of [commercial in confidence figure removed]. This estimate incorporates cost differences resulting from the displacement of tolcapone. Sensitivity analysis showed that the budget impact was sensitive to changes in opicapone uptake and tolcapone discontinuation rates with budget impact estimates between [commercial in confidence figure removed] and [commercial in confidence figure removed] in Year 1, increasing to between

[commercial in confidence figure removed] and [commercial in confidence figure removed] in Year 5.

Table 5. Company-reported costs associated with use of opicapone as second-line 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.

	2020	2021	2022	2023	2024
Sub-population of eligible patients (indication under consideration)	3005	3005	3005	3005	3005
Uptake of new medicine (%)	5%	10%	15%	20%	25%
Number of patients receiving new medicine allowing for discontinuations	137	259	434	601	751
Medicine acquisition costs in a market without new medicine	£2,438,715	£2,084,708	£1,927,372	£1,770,035	£1,770,035
Medicines acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition cost	¶¶	¶¶	¶¶	¶¶	¶¶
Net supportive medicines costs	£0	£0	£0	£0	£0
Net medicine acquisition costs (savings/costs) - including supportive medicines where applicable	¶¶	¶¶	¶¶	¶¶	¶¶

¶¶ commercial in confidence figure removed.

The company estimates that net resource implications arising from the introduction of opicapone will lead to a saving of [commercial in confidence figure removed] in year 1, decreasing to [commercial in confidence figure removed] in year 5. This is mainly a consequence of savings in monitoring cost required for liver monitoring with tolcapone. These resource-type savings are included for potential planning purposes but may not be realised in practice.

5.3 AWTTC critique

- The company assumes that Parkinson's disease prevalence and incidence remain stable over the 5-year period of the budget impact analysis. This contradicts the evidence they present to underpin their analysis that suggests that prevalence increased significantly in Wales between 2000 and 2016[36]. Omitting this increase in prevalence will cause bias. Further analysis provided by the company suggests that taking into account increasing prevalence[36] and population growth[38] will result in a total budget impact of [commercial in confidence figure removed] over all 5 years.

- Furthermore, omitting the addition of incident cases to the prevalence numbers over time underestimates monitoring costs for tolcapone, since incident patients will have more frequent monitoring in their first two years, which is not taken into account in the budget impact analysis. Therefore, liver monitoring costs for tolcapone would be higher than those presented.
- The company estimates that 25% of patients on levodopa will experience end-of-does motor fluctuation and are thus eligible for opicapone. However, considering that opicapone is positioned as second-line after entacapone, this will overestimate the number of eligible patients as only patients discontinuing entacapone would become eligible to receive opicapone.
- The company assumes that all eligible patients would receive tolcapone if opicapone was not available. This is highly unlikely considering the safety issues associated with tolcapone and the fact that it is rarely used in Wales. It is therefore likely that the budget impact analysis overestimates the number of patients on tolcapone, as many patients would have been on best supportive care before the introduction of opicapone. This has implications for the resource savings estimated.
- Due to lack of available data, treatment discontinuation rate is based on expert opinion rather than published evidence which introduces uncertainty in the patient numbers used to calculate the budget impact.

GLOSSARY

Hoehn and Yahr Scale[39]

The Hoehn and Yahr Scale describes how the motor symptoms of Parkinson's disease progress. It includes stages from 1 through to 5 plus intermediate stages 1.5 and 2.5. Stages indicate the relative level of disability:

- Stage 1: Unilateral symptoms only.
- Stage 1.5: Unilateral and axial involvement.
- Stage 2: Bilateral symptoms. No impairment of balance.
- Stage 2.5: Mild bilateral disease with recovery on pull test.
- Stage 3: Balance impairment. Mild to moderate disease. Physically independent.
- Stage 4: Severe disability, but still able to walk or stand unassisted.
- Stage 5: Needing a wheelchair or bedridden unless assisted.

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