IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-61

Opicapone (Parkinson disease) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Opicapon (Parkinsonkrankheit) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 22 December 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Opicapone (Parkinson disease) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
29 September 2016

Internal Commission No.:
A16-61

Address of publisher:
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Rudolf W. C. Janzen, Bad Homburg, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment[2]:

- Raphaela Gorris
- Thomas Kaiser
- Marco Knelangen
- Petra Kohlepp
- Christopher Kunigkeit
- Miriam Luhnen
- Anke Schulz
- Ulrike Seay

Keywords: opicapone, Parkinson disease, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

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[3] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
COMT	catechol-O-methyltransferase
DDCI	DOPA decarboxylase inhibitor
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LCIG	levodopa-carbidopa intestinal gel
PGIC	Patient Global Impression of Change
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
UPDRS	Unified Parkinson's Disease Rating Scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug opicapone. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 29 September 2016.

Research question

The aim of this report was to assess the added benefit of opicapone as adjunctive therapy to levodopa/DOPA decarboxylase inhibitors (DDCIs) in comparison with the appropriate comparator therapy (ACT) in adult patients with Parkinson disease and end-of-dose motor fluctuations who cannot be stabilized on those combinations.

Table 2 shows the research question of the benefit assessment of opicapone.

Table 2: Research question of the benefit assessment of opicapone

Therapeutic indication	**ACT**[a]
Adults with Parkinson disease and end-of-dose motor fluctuations who cannot be stabilized on levodopa/DDCI combinations	Adjunctive therapy with ▪ a non-ergot dopamine agonist or ▪ a **COMT inhibitor** or ▪ a MAO-B inhibitor If using all drug treatment options does not provide sufficient symptom control, **deep brain stimulation**[b] is to be considered.
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. b: For adults with idiopathic Parkinson disease and end-of-dose motor fluctuations who cannot be stabilized on levodopa/DDCI combinations and for whom deep brain stimulation or the use of a drug pump is an option, the company chose deep brain stimulation or apomorphine (administered with a drug pump) or LCIG as ACT. It did not present any data on these patients, however. ACT: appropriate comparator therapy; COMT: catechol-O-methyltransferase inhibitor; DDCI: DOPA decarboxylase inhibitor; G-BA: Federal Joint Committee; LCIG: levodopa-carbidopa intestinal gel; MAO-B: monoamine oxidase-B	

Following the G-BA, the company chose the catechol-O-methyltransferase (COMT) inhibitor entacapone as ACT. In addition, the company investigated one further research question: For adults with idiopathic Parkinson disease and end-of-dose motor fluctuations who cannot be stabilized on levodopa/DDCI combinations and for whom deep brain stimulation or the use of a drug pump is an option, it specified deep brain stimulation or apomorphine (administered

with a drug pump) or levodopa-carbidopa intestinal gel (LCIG) as ACT. However, the company presented no data for these patients.

The present assessment was conducted in comparison with the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit. This did not concur with inclusion criteria used by the company, which specified a minimum study duration of 3 months.

Results

The data presented by the company were unsuitable to draw conclusions on the added benefit of opicapone in comparison with the ACT.

The company identified one approval study of opicapone (study BIPARK I) including its one-arm extension phase. The BIPARK I study was a randomized active-controlled parallel-group study including adults with idiopathic Parkinson disease and end-of-dose fluctuations. In an initial double-blind phase, opicapone was compared with entacapone, each as adjunctive therapy to levodopa/DDCI preparations. The study duration of the double-blind phase was 14 to 15 weeks. In a subsequent, optional, open-label extension phase, patients from the double-blind phase could receive opicapone as adjunctive therapy to levodopa/DDCI preparations for 1 year. The extension phase had no control arm.

The randomized double-blind study phase with a study duration of only 14 to 15 weeks was not sufficiently long for the present benefit assessment. Parkinson disease is a chronic disease that requires long-term treatment. The duration of opicapone treatment is not limited. It is therefore necessary to base the benefit assessment of opicapone in comparison with the ACT on long-term effects.

The BIPARK I study presented by the company was already discussed in a different benefit assessment in the therapeutic indication of Parkinson disease, i.e. in the framework of an indirect comparison on the drug safinamide. Following IQWiG's dossier assessment on safinamide including the corresponding addendum, the G-BA decided that the BIPARK I study was unsuitable for the benefit assessment in the therapeutic indication of Parkinson disease due to a study duration of only 14 to 15 weeks.

In summary, no relevant data were available for the benefit assessment of opicapone in comparison with the ACT in adults with Parkinson disease and end-of-dose motor fluctuations.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug opicapone compared with the ACT is assessed as follows:

An added benefit of opicapone is not proven because the company presented no relevant data.

Table 3 presents a summary of the extent and probability of the added benefit of opicapone.

Table 3: Opicapone – extent and probability of added benefit

Therapeutic indication	ACT[a]	Extent and probability of added benefit
Adults with Parkinson disease and end-of-dose motor fluctuations who cannot be stabilized on levodopa/DDCI combinations	Adjunctive therapy with ▪ a non-ergot dopamine agonist or ▪ a **COMT inhibitor** or ▪ a MAO-B inhibitor If using all drug treatment options does not provide sufficient symptom control, **deep brain stimulation**[b] is to be considered.	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: For adults with idiopathic Parkinson disease and end-of-dose motor fluctuations who cannot be stabilized on levodopa/DDCI combinations and for whom deep brain stimulation or the use of a drug pump is an option, the company chose deep brain stimulation or apomorphine (administered with a drug pump) or LCIG as ACT. It did not present any data on these patients, however.
ACT: appropriate comparator therapy; COMT: catechol-O-methyltransferase inhibitor; DDCI: DOPA decarboxylase inhibitor; G-BA: Federal Joint Committee; LCIG: levodopa-carbidopa intestinal gel; MAO-B: monoamine oxidase-B

The G-BA decides on the added benefit.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit). For further details see [1,2].

2.2 Research question

The aim of this report was to assess the added benefit of opicapone as adjunctive therapy to levodopa/DDCIs in comparison with the ACT in adult patients with Parkinson disease and end-of-dose motor fluctuations who cannot be stabilized on those combinations.

Table 4 shows the research question of the benefit assessment of opicapone.

Table 4: Research question of the benefit assessment of opicapone

Therapeutic indication	**ACT**[a]
Adults with Parkinson disease and end-of-dose motor fluctuations who cannot be stabilized on levodopa/DDCI combinations	Adjunctive therapy with ▪ a non-ergot dopamine agonist or ▪ a **COMT inhibitor** or ▪ a MAO-B inhibitor If using all drug treatment options does not provide sufficient symptom control, **deep brain stimulation**[b] is to be considered.
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. b: For adults with idiopathic Parkinson disease and end-of-dose motor fluctuations who cannot be stabilized on levodopa/DDCI combinations and for whom deep brain stimulation or the use of a drug pump is an option, the company chose deep brain stimulation or apomorphine (administered with a drug pump) or LCIG as ACT (see Sections 2.7.1 and 2.7.2.3.2 of the full dossier assessment). It did not present any data on these patients, however. ACT: appropriate comparator therapy; COMT: catechol-O-methyltransferase inhibitor; DDCI: DOPA decarboxylase inhibitor; G-BA: Federal Joint Committee; LCIG: levodopa-carbidopa intestinal gel; MAO-B: monoamine oxidase-B	

Following the G-BA, the company chose the COMT inhibitor entacapone as ACT. In addition, the company investigated one further research question: For adults with idiopathic Parkinson disease and end-of-dose motor fluctuations who cannot be stabilized on levodopa/ DDCI combinations and for whom deep brain stimulation or the use of a drug pump is an option, it specified deep brain stimulation or apomorphine (administered with a drug pump) or LCIG as ACT. However, the company presented no data for these patients.

The present assessment was conducted in comparison with the ACT specified by the G-BA (see Sections 2.7.1 and 2.7.2.1 of the full dossier assessment).

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This did not concur with inclusion criteria used by the company, which specified a minimum study duration of 3 months.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on opicapone (status: 28 July 2016)
- bibliographical literature search on opicapone (last search on 28 July 2016)
- search in trial registries for studies on opicapone (last search on 4 August 2016)

To check the completeness of the study pool:

- search in trial registries for studies on opicapone (last search on 25 October 2016)

No additional relevant study was identified from the check.

With its information retrieval, the company identified one approval study of opicapone (study BIPARK I [3]) including its one-arm extension phase [4]. The BIPARK I study was unsuitable to derive conclusions on the added benefit of opicapone in comparison with the ACT. This is justified below.

The BIPARK I study was a randomized, active-controlled parallel-group study. Adult patients with idiopathic Parkinson disease and end-of-dose fluctuations were included in the study. In an initial double-blind phase, opicapone was compared with entacapone, each as adjunctive therapy to levodopa/DDCI preparations. A titration phase for the levodopa/DDCI dosage was followed by a treatment phase of 12 weeks under a stable dosage of the medications. The overall study duration of the double-blind phase was 14 to 15 weeks. In a subsequent, optional, open-label extension phase, patients from the double-blind phase could receive opicapone as adjunctive therapy to levodopa/DDCI preparations for 1 year. The extension phase had no control arm.

The randomized double-blind study phase with a study duration of only 14 to 15 weeks was not sufficiently long for the present benefit assessment. Parkinson disease is a chronic disease that requires long-term treatment. The duration of opicapone treatment is not limited. It is therefore necessary to base the benefit assessment of opicapone in comparison with the ACT on long-term effects.

The BIPARK I study presented by the company was already discussed in a different benefit assessment in the therapeutic indication of Parkinson disease, i.e. in the framework of an indirect comparison on the drug safinamide (dossier assessment on safinamide A15-18 [5] and corresponding addendum [6]). Following IQWiG's dossier assessment on safinamide including the corresponding addendum, the G-BA decided in the justification on its decision [7] that the BIPARK I study was unsuitable for the benefit assessment in the therapeutic indication of Parkinson disease due to a study duration of only 14 to 15 weeks. This decision

was made in the knowledge of the European Medicines Agency (EMA) Guideline [8] already effective at this time point (see also Section 2.7.2.1 of the full dossier assessment). Since the subsequent extension phase was a one-arm study, it can also not be used to balance benefit and harm of opicapone in comparison with the ACT because there was no comparator.

Irrespective of this, the company derived the added benefit based on an advantage of opicapone for the outcome "health status" (recorded with the Patient Global Impression of Change [PGIC]). However, the company presented no documents on the validity of PGIC in the therapeutic indication of Parkinson disease. The BIPARK I study showed no statistically significant differences between opicapone and entacapone for disease-specific morbidity outcomes (e.g. ON and OFF times, Unified Parkinson's Disease Rating Scale [UPDRS]) or for side effects.

In summary, no relevant data were available for the benefit assessment of opicapone in comparison with the ACT in adults with Parkinson disease and end-of-dose motor fluctuations.

2.4 Results on added benefit

No relevant data were available for the assessment of opicapone as adjunctive therapy to levodopa/DDCI preparations in adult patients with Parkinson disease and end-of-dose motor fluctuations who cannot be stabilized on those combinations. Hence there was no hint of an added benefit of opicapone in comparison with the ACT. An added benefit is therefore not proven.

2.5 Extent and probability of added benefit

The result of the assessment of the added benefit of opicapone in comparison with the ACT is summarized in Table 5.

Table 5: Opicapone – extent and probability of added benefit

Therapeutic indication	ACT[a]	Extent and probability of added benefit
Adults with Parkinson disease and end-of-dose motor fluctuations who cannot be stabilized on levodopa/DDCI combinations	Adjunctive therapy with ▪ a non-ergot dopamine agonist or ▪ a **COMT inhibitor** or ▪ a MAO-B inhibitor If using all drug treatment options does not provide sufficient symptom control, **deep brain stimulation**[b] is to be considered.	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: For adults with idiopathic Parkinson disease and end-of-dose motor fluctuations who cannot be stabilized on levodopa/DDCI combinations and for whom deep brain stimulation or the use of a drug pump is an option, the company chose deep brain stimulation or apomorphine (administered with a drug pump) or LCIG as ACT (see Sections 2.7.1 and 2.7.2.3.2 of the full dossier assessment). It did not present any data on these patients, however.
ACT: appropriate comparator therapy; COMT: catechol-O-methyltransferase inhibitor; DDCI: DOPA decarboxylase inhibitor; G-BA: Federal Joint Committee; LCIG: levodopa-carbidopa intestinal gel; MAO-B: monoamine oxidase-B

This deviates from the approach of the company, which derived a different added benefit for 2 patient groups: It derived a considerable added benefit for adults who are not yet eligible for deep brain stimulation or use of a drug pump (presented in Module 3 A and 4 A). It derived a non-quantifiable added benefit for adults who are eligible for deep brain stimulation or use of a drug pump (presented in Module 3 B and 4 B).

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

References for English extract

Please see full dossier assessment for full reference list.

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