IQWiG Reports – Commission No. A18-68

Ocriplasmin (vitreomacular traction) –

Benefit assessment according to §35a Social Code Book V[1] (expiry of the decision)

Extract

[1] Translation of the executive summary of the dossier assessment *Ocriplasmin (vitreomakuläre Traktion) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 1 March 2019). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) 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 ocriplasmin. This is a reassessment after expiry of the decision dated 17 October 2013. A time limit was imposed on the decision because it remained unclear whether the advantages observed under ocriplasmin treatment will be sustained in the long term. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 12 October 2018.

Research question

The aim of this report is to assess the added benefit of ocriplasmin in comparison with the appropriate comparator therapy (ACT) for treating vitreomacular traction (VMT) in adults, including when associated with a macular hole of diameter ≤ 400 µm.

The research questions presented in Table 2 result from the ACT specified by the G-BA.

Table 2[2]: Research questions of the benefit assessment of ocriplasmin

Research question	Indication	ACT[a]
	Vitreomacular traction, including when associated with a macular hole of diameter ≤ 400 µm:	
1	Adults with mild symptoms (e.g. slight worsening of visual acuity, minor visual impairment, no progression of symptoms)	Watchful waiting
2	Adults with severe symptoms (e.g. progressive deterioration of visual acuity, progressive retinal changes, progressive visual impairment)	Pars plana vitrectomy
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA further stated that the approval of ocriplasmin did not exclude use in asymptomatic VMT. According to the generally acknowledged state of medical science, however, a therapeutic intervention was argued to not be medically indicated in the asymptomatic VMT scenario. Therefore, the group of patients with asymptomatic VMT was to be excluded from this benefit assessment of ocriplasmin.

The company followed the G-BA's specification of the ACT.

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

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

duration of 24 weeks were used for deriving any added benefit. This corresponds to the company's inclusion criteria.

Results on research question 1: Patients with mild symptoms

For the benefit assessment, 5 relevant studies were available: TG-MV-004, TG-MV-006, TG-MV-007, J-12-075, and TG-MV-014. The studies TG-MV-004, TG-MV-006, and TG-MV-007 were already used as the basis of the prior benefit assessment of ocriplasmin. In this dossier, the company additionally presented the 2 studies J-12-075 and TG-MV-014.

Study design

The 5 studies presented by the company are randomized, double-blind, controlled, parallel-group, multicentric studies.

Each study included patients with symptomatic focal vitreomacular adhesion (VMA, corresponds to VMT). Patients were randomly allocated to the intervention arm, which involved one injection of ocriplasmin, or to the control arm, which involved one injection of placebo (TG-MV-006 and TG-MV-007) or one sham injection (TG-MV-004, J-12-075, TG-MV-014). The treatment with ocriplasmin was as approved. The placebo and sham injections in the control arm are an adequate implementation of the ACT.

Patients were followed up after the ocriplasmin injection or the sham or placebo injection. It was possible to perform pars plana vitrectomy upon the investigator's discretion as of Day 28 after injection, or earlier in case of disease deterioration.

The primary outcome of the studies is the nonsurgical resolution of VMT on Day 28 after injection (or Day 14 after injection in the TG-MV-004 study). Secondary outcomes comprise symptoms, health-related quality of life, and adverse events.

The studies had a duration of 6 months, except for TG-MV-014, where patients were followed up for 24 months. This benefit assessment is based on the results of the 5 included studies at Month 6 and the results of the long-term study TG-MV-014 at Month 24. Where no usable data were available for Month 24 of TG-MV-014, the analyses at Month 12 would be used alternatively.

Subpopulation relevant for the research question

In accordance with the approval, ocriplasmin is to be used only for treating patients with VMT associated with a macular hole ≤ 400 µm in diameter. To answer the present research question, the study population with mild symptoms at the start of the study is relevant.

Patients treated off label and patients with severe symptoms (operationalized by visual acuity; decimal value < 0.1, corresponding to < 35 letters of the Early Treatment Diabetic Retinopathy Study [ETDRS]) made up < 20% of the population of the presented studies. For this benefit assessment, the total populations of the studies were therefore used.

Risk of bias and reliability

The risk of bias on the study level was rated as high for the TG-MV-004 study. For the studies TG-MV-006, TG-MV-007, J-12-075, and TG-MV-014, the risk of bias at study level was rated as low.

For the TG-MV-004 study, the high risk of bias at study level alone results in a high risk of bias at outcome level for all outcomes. The risk of bias at outcome level is rated as low for the relevant outcomes of the studies TG-MV-006, TG-MV-007, J-12-075, and TG-MV-014 (at Month 6). The only exception is the high risk of bias for health-related quality of life (measured using the National Eye Institute 25-item Visual Function Questionnaire [NEI VFQ-25] at Month 6 of the TG-MV-014 study. The results of all outcomes of the TG-MV-014 study also have a high risk of bias at Month 12 or 24.

Irrespective of the risk of bias, there are limitations in terms of the definition of the relevant patient population as well as the study design, which, all things considered, reduced the certainty of conclusion. Firstly, it is unclear whether the total population of the included studies is, in fact, adequate for answering this research question. The patient population with mild symptoms, which is relevant for the research question, is defined solely by visual acuity. As already discussed in the initial assessment procedure, it is unclear whether this is sufficient as the sole criterion. Secondly, a limitation arises from the included studies' designs. From Day 28 after injection, pars plana vitrectomy was possible at any time (before, it was only possible in case of deterioration of disease status). The decision to perform vitrectomy was made at the discretion of the treating investigator rather than on the basis of an indication according to pre-defined criteria. This could lead to the investigators weighing the need for vitrectomy on the basis of different criteria or delaying the procedure until the end of the study.

Overall, these limitations reduced the certainty of conclusions as they did in the initial assessment procedure for ocriplasmin.

Analyses at Month 6

On the basis of the available data, a metaanalysis of the 5 studies can be used to derive at most indications, for example of an added benefit, for all outcomes due to the limited certainty of conclusions.

Mortality

All-cause mortality

For the outcome of all-cause mortality, the metaanalysis does not show a statistically significant difference between treatment arms. Consequently, there is no hint of added benefit of ocriplasmin in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Improvement of visual acuity (≥ 2 lines)

For the outcome of improvement of visual acuity by ≥ 2 lines (corresponds to ≥ 2 ETDRS letters), the metaanalysis shows a significant difference between treatment arms to the advantage of ocriplasmin. For the outcome of improvement of visual acuity, this results in an indication of added benefit of ocriplasmin in comparison with watchful waiting.

Vitrectomy

For the outcome of vitrectomy, the metaanalysis shows a statistically significant difference between treatment arms in favour of ocriplasmin. This results in an indication of added benefit of ocriplasmin in comparison with watchful waiting.

Metamorphopsia

No usable data are available for this outcome.

Health-related quality of life

NEI VFQ-25

For the sum score of NEI VFQ-25, the mean difference between the start of the study and the end or Month 6 was used. In the metaanalysis, there was a statistically significant difference in favour of ocriplasmin. The 95% CI of the standardized mean difference (Hedges g) is, however, not fully outside the irrelevance range of -0.2 to 0.2. Hence, it is not possible to rate the observed effect as relevant. Consequently, there is no hint of added benefit of ocriplasmin in comparison with watchful waiting; an added benefit is therefore not proven.

Adverse events

SAEs

For the outcome of SAEs, the metaanalysis does not show a statistically significant difference between treatment groups. Consequently, there is no hint of greater or lesser harm of ocriplasmin in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Cataract (combination of PTs)

For the outcome of cataract, the metaanalysis does not show a statistically significant difference between treatment arms. Consequently, there is no hint of greater or lesser harm of ocriplasmin in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Eye disorders (SOC), photopsia (PT), vitreous floaters (PT), changed vision (combination of PTs)

For the outcomes of eye disorders, photopsia, vitreous floaters, and visual changes, each of the respective metaanalyses shows a statistically significant difference to the disadvantage of ocriplasmin. This results in a hint of greater harm of ocriplasmin for each of these outcomes.

Analyses at Month 24

Given the limited certainty of conclusions and high risk of bias for all outcomes, no more than hints, for example of an added benefit, can be derived from the available data of the TG-MV-014 study at Month 24.

Mortality

All-cause mortality

For the outcome of all-cause mortality, no statistically significant difference between treatment arms was found. Consequently, there is no hint of added benefit of ocriplasmin in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Improvement of visual acuity (≥ 2 lines)

For the outcome of improvement of visual acuity by ≥ 2 lines (corresponds to ≥ 10 ETDRS letters), no statistically significant difference between treatment arms was found. Consequently, there is no hint of added benefit of ocriplasmin in comparison with watchful waiting; an added benefit is therefore not proven.

Vitrectomy

For the outcome of vitrectomy, no statistically significant difference between treatment arms was found. Consequently, there is no hint of added benefit of ocriplasmin in comparison with watchful waiting; an added benefit is therefore not proven.

Metamorphopsia

For the outcome of metamorphopsia, no usable data were available.

Health-related quality of life

NEI VFQ-25

For the sum score of the NEI VFQ-25, the mean difference between the start of the study and the end of the study was analysed. Due to the high percentage of patients excluded from analysis (> 30%), the results at Month 24 are not usable. Therefore, the results at Month 12 were used for the benefit assessment.

No statistically significant difference between treatment arms was found. Consequently, there is no hint of added benefit of ocriplasmin in comparison with watchful waiting; an added benefit is therefore not proven.

Adverse events

SAEs

For the outcome of SAEs, no statistically significant difference between treatment arms was found. Consequently, there is no hint of greater or lesser harm of ocriplasmin in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Cataract (combination of PTs)

For the outcome of cataract, no statistically significant difference between treatment arms was found. Consequently, there is no hint of greater or lesser harm of ocriplasmin in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Dyschromatopsia (combination of PTs), photophobia (PT), photopsia (PT), vitreous floaters (PT)

For each of the outcomes of dyschromatopsia, photophobia, and vitreous floaters, there is a statistically significant disadvantage of ocriplasmin. For each of these outcomes, this results in a hint of greater harm of ocriplasmin in comparison with watchful waiting.

Results on research question 2: Patients with severe symptoms

For VMT patients with severe symptoms, no data were available to assess the added benefit of ocriplasmin in comparison with the ACT. An added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of added benefit of the drug ocriplasmin in comparison with the ACT are assessed as follows:

Research question 1: Patients with mild symptoms

All things considered, the results after 6 months of follow-up reveal positive effects of ocriplasmin for the outcomes of vitrectomy and improvement of visual acuity, which are contrasted by negative effects for various AEs on eye disorders. After 24 months of follow-up, similar effect sizes as those seen at Month 6 are found for the outcomes of vitrectomy and improvement of visual acuity, but they are not statistically significant. While the negative effects of ocriplasmin continue to be statistically significant, they did not deteriorate as a result of the longer follow-up.

The G-BA limited the validity period of the most recent decision on ocriplasmin due to missing long-term data, particularly on the reduction of cataract development and health-related quality of life. The long-term data (after 12 or 24 months) show no difference between ocriplasmin and watchful waiting for either of these two outcomes. Therefore, all things considered, there is no hint of added benefit of ocriplasmin in comparison with the ACT of watchful waiting for

[3] 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, added benefit not proven, or less benefit). For further details see [1,2].

patients with VMT with a macular hole diameter ≤ 400 µm and mild symptoms; an added benefit is therefore not proven.

Research question 2: Patients with severe symptoms

Since the company did not present any data for assessing the added benefit of ocriplasmin in comparison with the ACT in patients with VMT with a macular hole diameter ≤ 400 µm and severe symptoms, an added benefit of ocriplasmin is not proven for these patients.

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

Table 3: Ocriplasmin – probability and extent of added benefit

Research question	**Indication**	**ACT[a]**	**Probability and extent of added benefit**
	Vitreomacular traction, including when associated with a macular hole of diameter ≤ 400 µm:		
1	Adults with mild symptoms (e.g. slight worsening of visual acuity, minor visual impairment, no progression of symptoms)	Watchful waiting	Added benefit not proven
2	Adults with severe symptoms (e.g. progressive deterioration of visual acuity, progressive retinal changes, progressive visual impairment)	Pars plana vitrectomy	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee			

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

Note:

An addendum (A19-20) to dossier assessment A18-68 has been published.

References for English extract

Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-68-ocriplasmin-vitreomacular-traction-including-when-associated-with-macular-hole-benefit-assessment-according-to-35a-social-code-book-v-reassessment-after-expiry-of-the-decision.10757.html.