IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Aflibercept (Eylea) –

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

Extract

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IQWiG thanks the medical and scientific advisor for her contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect her opinion.

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AMD	age-related macular degeneration
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)
RCT	randomized controlled trial
SAE	serious adverse event
SGB	*Sozialgesetzbuch* (Social Code Book)

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 aflibercept. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to “the company”). The dossier was sent to IQWiG on 17.12.2012.

Research question

The aim of this report is to assess the added benefit of aflibercept compared with ranibizumab as appropriate comparator therapy (ACT) in adult patients with wet age-related macular degeneration (AMD).

The assessment was based on patient-relevant outcomes.

No relevant study was identified where the ACT ranibizumab was used according to its approval status. Other analyses presented by the company could not be used for the benefit assessment as they did not allow to compare the benefit of aflibercept and ranibizumab. These analyses include an unpublished mathematical simulation by the manufacturer of ranibizumab from an assessment report of the European Medicines Agency (EMA), as well as extrapolations made by the company on the risk of an ocular adverse event (AE) of each intravitreal injection, and an analysis called "descriptive indirect comparison".

Results

To conduct a benefit assessment despite the lack of relevant studies, the company chose the approach described below. First, the company presented the results of the two approval studies of aflibercept (VIEW 1 and VIEW 2) although ranibizumab was not used according to its approval status in these studies. It stated that equivalent clinical efficacy of aflibercept in comparison with ranibizumab was to be derived from these studies. This statement was included in a "descriptive indirect comparison" conducted by the company. It did not draw a conclusion on the added benefit on the basis of these studies.

Furthermore, the company described an unpublished mathematical simulation by the manufacturer of ranibizumab from an assessment report of EMA, which was done with the aim to revise the treatment regimen of ranibizumab. From this simulation, it adopted the assumption that the approval-compliant use of ranibizumab leads to an average of 8.4 injections in the first year. In addition, the company assumed that each intravitreal injection carries the same risk of an ocular AE. The company considered endophthalmitis as an example of ocular AEs, and estimated that the mean rate of endophthalmitis was 0.044% "after any substance administered intravitreally". On the basis of this, it calculated the expected number of cases of endophthalmitis under aflibercept and ranibizumab, postulating

that fewer AEs caused by intravitreal injection occurred under aflibercept in the first year of treatment because more injections are performed under ranibizumab (8.4 on average) than under aflibercept (7, as derived by the company from the approval). The company did not support this conclusion with study data. The results of the VIEW studies even contradicted this assumption. In addition, aflibercept was administered 7.5 times on average in the VIEW studies during the first year of the study. This discrepancy to the company's assumption based on the approval is due to the administration according to weeks in the VIEW studies (4 weeks = 1 month). Hence, according to the approval, up to 8 injections with aflibercept are possible in the first year of the treatment.

The company finally conducted a "descriptive indirect comparison" on the basis of these assumptions, performing a balancing of the benefits and harms, which was not based on outcomes.

In summary, the company derived a non-quantifiable added benefit of aflibercept versus ranibizumab. This was justified with a reduction of necessary intravitreal injections and the resulting reduction of AEs associated with the injection as well as a "harm-benefit profile improved by about 20%".

This result was not accepted as the "descriptive indirect comparison" did not fulfil the criteria for an adjusted indirect comparison, and was also not based on outcomes. Assessing patient-relevant outcomes is necessary, however, to be able to balance the positive and negative effects. It was also unclear what exactly was meant by a "harm-benefit profile improved by about 20%", and what impact this result has for patients treated with aflibercept or ranibizumab. Moreover, the company's assumption that a higher number of injections inevitably leads to more ocular AEs under ranibizumab in comparison with aflibercept was not comprehensible based on the two approval studies for aflibercept VIEW 1 and VIEW 2.

In summary, due to the flaws described above, it is not possible to make a valid assessment of the added benefit of aflibercept in comparison with ranibizumab on the basis of the evidence provided in Module 4 of the dossier. Overall, the data provided could not be used for a benefit assessment.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[3]

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

No proof of added benefit of aflibercept in comparison with the ACT specified by the G-BA could be derived from the data presented. Hence there are no patient groups for whom a therapeutically important added benefit could be derived.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The decision on added benefit is made by the G-BA.

2.2 Research question

The benefit assessment of aflibercept was conducted according to the approval status [3] for the treatment of adults with neovascular (wet) AMD.

The G-BA specified ranibizumab as ACT, and the company concurred with this specification. Hence this assessment was conducted in comparison with ranibizumab.

The assessment was conducted based on patient-relevant outcomes.

Further information about the research question can be found in Module 3, Section 3.1 and Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

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

- Studies on aflibercept completed by the company up to 11.12.2012 (study list of the company)
- Results of a search in bibliographical databases and trial registries for studies on aflibercept (last search 17.10.2012 in bibliographical databases, and 25.10.2012 in trial registries, searches by the company)
- Results of a bibliographical literature search and a search in trial registries for randomized controlled trials (RCTs) and non-RCTs on the ACT ranibizumab (last search 17.10.2012 in bibliographical databases, and 23.10.2012 in trial registries, searches by the company).

[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 1-3 cannot be drawn from the available data), see [1]. 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), see [2].

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

No relevant study was identified from the steps of information retrieval mentioned. A comparison with the ACT ranibizumab was performed in the approval studies of aflibercept, but ranibizumab was not used according to its approval status [4,5]. According to its approval status, treatment with ranibizumab is provided monthly and continued until maximal visual acuity is attained. This is regarded to be the case if the visual acuity of a patient remains stable for 3 consecutive monthly controls [6]. No additional studies with approval-compliant use of ranibizumab, which might have been suitable for an indirect comparison, were available.

Other analyses presented by the company could not be used for the benefit assessment as they did not allow to compare the benefit of aflibercept and ranibizumab. These analyses include an unpublished mathematical simulation by the manufacturer of ranibizumab from an assessment report of EMA [7], as well as extrapolations made by the company on the risk of an ocular AE of each intravitreal injection, and a so-called "descriptive indirect comparison".

The company's analyses, approach, and results, will be described in Section 2.4, and reasons will be given why these could not be used for the benefit assessment.

2.4 Results on added benefit

No relevant studies or otherwise evaluable data were available for the research question of the benefit assessment. Hence there is no proof of added benefit of aflibercept versus the ACT ranibizumab specified by the G-BA.

To conduct a benefit assessment despite the lack of relevant studies, the company chose the approach described below:

- The company presented the results although the approval studies of aflibercept VIEW 1 and VIEW 2 [4,5] were not relevant for the benefit assessment because ranibizumab was not used according to its approval status. It stated that comparable results of aflibercept and ranibizumab were observed in all outcomes related to vision and morphology, and derived equivalent clinical efficacy. This statement was included in a "descriptive indirect comparison" conducted by the company. It did not draw a conclusion on the added benefit on the basis of these studies.
- The company presented an unpublished mathematical simulation by the manufacturer of ranibizumab from an EMA assessment report, which is the best available evidence from the company's point of view. This simulation was conducted on the basis of studies on ranibizumab to adapt the treatment regimen of ranibizumab. The current treatment regimen entails an average of 8.4 injections in the first year of the treatment according to the simulation.

- In addition, the company stated that each intravitreal injection carries the same risk of an ocular AE. The company considered endophthalmitis as an example of ocular AEs. Based on a literature search, it estimated that the mean rate of endophthalmitis was 0.044% "after any substance administered intravitreally", and calculated the expected number of cases of endophthalmitis under aflibercept and ranibizumab as an example. Hence the company postulated that fewer AEs caused by intravitreal injection occurred under aflibercept in the first year of treatment because more injections are performed under ranibizumab (8.4 on average) than under aflibercept (7, as derived by the company from the approval).
- The company finally conducted a so-called "descriptive indirect comparison" on the basis of these assumptions and data, performing a balancing of the benefits and harms, which was not based on outcomes.

The result of the company was a non-quantifiable added benefit of aflibercept versus ranibizumab. This was justified with a reduction of necessary intravitreal injections and the cumulative reduction of associated AEs as well as a "harm-benefit profile improved by about 20%".

This approach was not accepted in this dossier assessment. No valid conclusions on the added benefit of aflibercept can be drawn from the analyses presented by the company. For instance, the "descriptive indirect comparison" conducted by the company did not fulfil the criteria for an adjusted indirect comparison. The "descriptive indirect comparison" was also not based on outcomes, which would have been relevant for deriving a conclusion on added benefit. It was also unclear what exactly was meant by a "harm-benefit profile improved by about 20%", and what impact this result has for patients treated with aflibercept or ranibizumab. Moreover, the assumption that a higher rate of intravitreal AEs is inevitable under ranibizumab was not comprehensible based on the VIEW studies (in relation to ocular AEs in the study eye, serious AEs (SAEs) and study discontinuations due to AEs). No benefit of aflibercept versus ranibizumab could be derived from these studies although ranibizumab was not used according to its approval status and adapted to visual acuity (8.4 injections on average), but considerably more often (12.3 injections on average), in the first year. In addition, in accordance with its approval status, 7.5 injections of aflibercept were administered on average in the VIEW studies in the first year of the treatment. The discrepancy to the company's assumption of 7 injections based on the approval of aflibercept is due to the administration according to weeks in the VIEW studies (4 weeks = 1 month). Hence up to 8 injections with aflibercept are possible in the first year of the treatment. The expected difference in injection frequency in approval-compliant use of the two substances can therefore be neglected and cannot be separated from direct substance-specific AEs. Detailed comments on the company's approach can be found in Section 2.7.2.7 of the full dossier assessment.

In summary, due to the flaws described above, it is not possible to make a valid assessment of the added benefit of aflibercept in comparison with ranibizumab on the basis of the evidence

provided in Module 4 of the dossier. Overall, the data provided could not be used for a benefit assessment. An added benefit of aflibercept is not proven.

Further information on the results on added benefit can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.3 of the dossier and in Sections 2.7.2.4 and 2.7.2.7 of the full dossier assessment.

2.5 Extent and probability of added benefit

No proof of added benefit of aflibercept in comparison with the ACT specified by the G-BA could be derived from the data presented. Hence there are no patient groups for whom a therapeutically important added benefit could be derived.

This assessment deviates from that of the company, which derived a non-quantifiable added benefit of aflibercept versus the ACT ranibizumab. The company did not make a statement about the probability of the added benefit.

The decision on added benefit is made by the G-BA.

2.6 List of included studies

Not applicable as the company did not present any study data in Module 4 of the dossier from which an added benefit of aflibercept versus the ACT specified by the G-BA could be derived.

References for English extract

Please see full dossier assessment for full reference list.

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