Eplontersen (hereditary transthyretin amyloidosis with polyneuropathy)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Eplontersen (hereditäre Transthyretin-Amyloidose mit Polyneuropathie) – Nutzenbewertung gemäß § 35a SGB V*. 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.

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Keywords

Eplontersen, Amyloid Neuropathies, Benefit Assessment

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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.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ATTRv amyloidosis	hereditary transthyretin amyloidosis
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
SGB	Sozialgesetzbuch (Social Code Book)

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 eplontersen. 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 28 April 2025.

Research question

The aim of this report is to assess the added benefit of eplontersen in comparison with vutrisiran the appropriate comparator therapy (ACT) in adult patients with hereditary transthyretin amyloidosis (ATTRv amyloidosis) with stage 1 or stage 2 polyneuropathy.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of eplontersen

Therapeutic indication	**ACT**[a]
Adults with ATTRv amyloidosis with stage 1 or stage 2 polyneuropathy	Vutrisiran[b]
a. Presented is the ACT specified by the G-BA. b. It is assumed that in both study arms a patient-specific adequate treatment of the respective organ manifestation (such as cardiac failure and/or polyneuropathy) corresponding to the current state of medical knowledge is conducted, taking into account the special characteristics of the disease ATTRv amyloidosis, and that this is documented as concomitant treatment. ACT: appropriate comparator therapy; ATTRv amyloidosis: hereditary transthyretin amyloidosis; G-BA: Federal Joint Committee	

The company followed the 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 duration of 24 weeks were used to derive the added benefit. This concurred with the company's inclusion criteria.

Results

Concurring with the company, the review of the completeness of the study pool did not identify any studies for the direct comparison of eplontersen with the ACT in the given therapeutic indication.

As no directly comparative RCT versus the ACT was available, the company searched for directly comparative RCTs without restricting the search to the ACT. It identified the NEURO-TTRansform pivotal study and, based on the data from this study, presented a comparison between eplontersen and inotersen in the present therapeutic indication. The company assumed that the data presented for the comparison of eplontersen versus inotersen allowed conclusions to be drawn about the classification of the added benefit versus the ACT vutrisiran. However, the company did not support this assumption with data. The company's approach was not appropriate.

The data presented by the company were not suitable for drawing conclusions on the added benefit of eplontersen compared with the ACT in adult patients with ATTRv amyloidosis with stage 1 or stage 2 polyneuropathy. The comparator therapy in the comparison used by the company does not concur with the ACT, meaning that no data was available for comparing eplontersen with the comparator therapy specified by the G-BA.

Results on added benefit

No suitable data were available for assessing the added benefit of eplontersen versus the ACT in adult patients with ATTRv amyloidosis with stage 1 or stage 2 polyneuropathy. There was no hint of an added benefit of eplontersen 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]

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

[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].

Table 3: Eplontersen – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with ATTRv amyloidosis with stage 1 or stage 2 polyneuropathy	Vutrisiran[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. It is assumed that in both study arms a patient-specific adequate treatment of the respective organ manifestation (such as cardiac failure and/or polyneuropathy) corresponding to the current state of medical knowledge is conducted, taking into account the special characteristics of the disease ATTRv amyloidosis, and that this is documented as concomitant treatment.

ACT: appropriate comparator therapy; ATTRv amyloidosis: hereditary transthyretin amyloidosis; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of eplontersen in comparison with vutrisiran as the ACT in adult patients with ATTRv amyloidosis with stage 1 or stage 2 polyneuropathy.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of eplontersen

Therapeutic indication	**ACT**[a]
Adults with ATTRv amyloidosis with stage 1 or stage 2 polyneuropathy	Vutrisiran[b]
a. Presented is the ACT specified by the G-BA. b. It is assumed that in both study arms a patient-specific adequate treatment of the respective organ manifestation (such as cardiac failure and/or polyneuropathy) corresponding to the current state of medical knowledge is conducted, taking into account the special characteristics of the disease ATTRv amyloidosis, and that this is documented as concomitant treatment. ACT: appropriate comparator therapy; ATTRv amyloidosis: hereditary transthyretin amyloidosis; G-BA: Federal Joint Committee	

The company followed the 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. RCTs with a minimum duration of 24 weeks were used to derive the added benefit. This concurred with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on eplontersen (status: 18 February 2025)
- Bibliographical literature search on eplontersen (last search on 17 March 2025)
- Search of trial registries/trial results databases for studies on eplontersen (last search on 17 March 2025)
- Search on the G-BA website for eplontersen (last search on 17 March 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on eplontersen (last search on 12 May 2025); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the review of the completeness of the study pool did not identify any studies for the direct comparison of eplontersen with the ACT in the given therapeutic indication.

As no directly comparative RCT versus the ACT was available, the company searched for directly comparative RCTs without restricting the search to the ACT. It identified the NEURO-TTRansform pivotal study [3] and, based on the data from this study, presented a comparison between eplontersen and inotersen in the given therapeutic indication. From the comparison with inotersen presented, the company drew conclusions about the added benefit of eplontersen versus the ACT vutrisiran (see following section).

Data presented by the company

Adult patients with ATTRv amyloidosis with stage 1 or stage 2 polyneuropathy were enrolled in the NEURO-TTRansform study. The patients were allocated in a ratio of 6:1 to treatment with eplontersen (N = 144) or inotersen (N = 24). The aim of the study was to compare eplontersen with placebo using an external placebo control from the NEURO-TTR study [4]. NEURO-TTR is an RCT comparing inotersen with placebo in the same therapeutic indication. The comparison of eplontersen versus inotersen in the NEURO-TTRansform study was not planned, according to the study protocol.

In its dossier, the company presented the post hoc comparison between eplontersen and inotersen conducted for the NEURO-TTRansform study and derived an indication of a considerable added benefit of eplontersen versus inotersen. Due to the lack of studies of direct comparison with the ACT, the company deduced a hint of a non-quantifiable added

benefit versus the ACT vutrisiran based on the results of the comparison with inotersen. The company justified this approach by stating that inotersen, like the ACT vutrisiran, belongs to the 'silencer' drug class. It assumed that the data presented for the comparison of eplontersen versus inotersen allowed conclusions to be drawn about the classification of the added benefit versus the ACT vutrisiran. However, company did not support this assumption with data. The company's approach was not appropriate.

Assessment of the data presented by the company

The data presented by the company are not suitable for drawing conclusions on the added benefit of eplontersen compared with the ACT in adult patients with ATTRv amyloidosis with stage 1 or stage 2 polyneuropathy. The comparator therapy used in the comparison by the company does not concur with the ACT, meaning that no data was available for comparing eplontersen with the comparator therapy specified by the G-BA.

I 4 Results on added benefit

No suitable data were available for assessing the added benefit of eplontersen versus the ACT in adult patients with ATTRv amyloidosis with stage 1 or stage 2 polyneuropathy. There is no hint of an added benefit of eplontersen in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

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

Table 5: Eplontersen – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with ATTRv amyloidosis with stage 1 or stage 2 polyneuropathy	Vutrisiran[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. It is assumed that in both study arms a patient-specific adequate treatment of the respective organ manifestation (such as cardiac failure and/or polyneuropathy) corresponding to the current state of medical knowledge is conducted, taking into account the special characteristics of the disease ATTRv amyloidosis, and that this is documented as concomitant treatment.

ACT: appropriate comparator therapy; ATTRv amyloidosis: hereditary transthyretin amyloidosis; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which, based on a comparison of eplontersen with inotersen, derived a hint of non-quantifiable added benefit versus the ACT vutrisiran.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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