IQWiG Reports – Commission No. A21-32

Avatrombopag (primary chronic immune thrombocytopenia) –

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

Extract

[1] Translation of Sections 2.1 to 2.4 of the dossier assessment *Avatrombopag (primäre chronische Immunthrombozytopenie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 June 2021). 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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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.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITP	immunothrombocytopaenia
RCT	randomized controlled trial
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 avatrombopag. 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 22 March 2021.

Research question

The aim of this report is to assess the added benefit of avatrombopag in comparison with eltrombopag or romiplostim as the appropriate comparator therapy (ACT) in adult patients with primary chronic thrombocytopaenia who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of avatrombopag

Indication	ACT[a]
Treatment of primary chronic ITP in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)	Eltrombopag or romiplostim

a. Presented is the respective ACT specified by the G-BA.
b. For this indication, patients are assumed to require medical treatment and to be refractory mainly to corticosteroids.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; ITP: immunothrombocytopaenia

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of added benefit.

Results

No relevant study was identified for assessing the added benefit of avatrombopag in comparison with the ACT.

The company reported that it, too, had been unable to identify any relevant study. Nevertheless, it submitted RCTs 302 and 305. The 302 study is an exclusively placebo-controlled RCT. It is unsuitable for deriving an added benefit. The 305 study compared avatrombopag with eltrombopag but was terminated early and is presented by the company as supplementary information only. It is also irrelevant for the benefit assessment.

Hence, the company has not submitted any suitable data for assessing any added benefit of avatrombopag in comparison with the ACT specified by the G-BA. Consequently, there is no hint of added benefit of avatrombopag 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 presented results, the probability and extent of added benefit of the drug avatrombopag in comparison with the ACT have been assessed as follows:

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

Table 3: Avatrombopag – probability and extent of added benefit

Indication	ACT[a]	Probability and extent of added benefit
Treatment of primary chronic ITP in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)[b]	Eltrombopag or romiplostim	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. For this indication, patients are assumed to require medical treatment and to be refractory mainly to corticosteroids.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; ITP: immunothrombocytopaenia

The G-BA decides on the added benefit.

[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].

2.2 Research question

The aim of this report is to assess the added benefit of avatrombopag in comparison with eltrombopag or romiplostim as the ACT in adult patients with primary chronic immunothrombocytopaenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of avatrombopag

Indication	**ACT**[a]
Treatment of primary chronic ITP in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)[b]	Eltrombopag or romiplostim
a. Presented is the respective ACT specified by the G-BA. b. For this indication, patients are assumed to require medical treatment and to be refractory mainly to corticosteroids. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; ITP: immunothrombocytopaenia	

The company designated eltrombopag and romiplostim as the ACT, thus following the G-BA's specifications.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- Study list on avatrombopag (as of 4 January 2021)
- Bibliographic literature search on avatrombopag (most recent search on 23 February 2021)
- Search in trial registries / study results databases on avatrombopag (most recent search on 11 March 2021)
- Search on the G-BA website on avatrombopag (most recent search on 4 January 2021)

To check the completeness of the study pool:

- Search in trial registries for studies on avatrombopag (most recent search on 30 March 2021); see Appendix A of the full dossier assessment for search strategies

The check did not reveal any relevant studies for assessing the added benefit of avatrombopag in comparison with the ACT.

Study pool of the company

The company reported that it, too, had been unable to identify any relevant study. Nevertheless, it included studies 302 and 305 in its study pool.

Study 302

The 302 study [3] is a placebo-controlled RCT. It included adult patients with primary chronic ITP who had received prior treatment with 1 or more ITP therapies (including, but not limited to, corticosteroids and immunoglobulins). Patients were randomized to treatment with avatrombopag (N = 32) or placebo (N = 17) in a 2:1 ratio. The planned randomized study duration was 26 weeks. Considering the 302 study to represent the best available evidence, the company submitted the full study characteristics and results of the 302 study in Module 4 B of its dossier.

The study offers no comparison with the ACT and is therefore irrelevant for the assessment of added benefit.

Study 305

The 305 study [4] is an RCT comparing avatrombopag with eltrombopag. It included adult patients with primary chronic ITP and prior treatment with 1 or more ITP therapies (including, but not limited to corticosteroids and immunoglobulins). The planned study duration was 6 months. In the company's view, the 305 study meets all inclusion criteria for the benefit assessment. However, the study was terminated early due to enrolment challenges. In Module 4 B, the company did not submit any detailed information on the study design or study population. The company presented the results of the 305 study only as supplementary information and in the form of a summary text.

Since the study was terminated early and therefore does not meet the minimum study duration of 24 weeks, it is irrelevant for the assessment of added benefit. Furthermore, in Module 4 B of the dossier, the study data have not been prepared in accordance with the requirements of dossier templates, and further evaluation of the study is impossible due to missing information.

Inappropriate derivation of added benefit by the company

The company used both 302 and 305 for deriving added benefit. In Module 4 B, the company further stated that an independent network metaanalysis was undertaken to compare the effectiveness of avatrombopag versus eltrombopag. The company added that, for this purpose, predefined, platelet-associated outcomes were used in comparable patient populations. The data were based (1) on the pivotal phase III study and the supportive phase II and phase III studies on avatrombopag and (2) on 6 different studies on eltrombopag. The company discussed this analysis outside the results section and submitted data only for the outcome of "cumulative number of weeks with platelet response".

In this section of its dossier, the company also compared the data from the pivotal studies of avatrombopag, eltrombopag, and romiplostim. For individual placebo-controlled studies, the company presented data only descriptively and for the outcomes of "cumulative number of weeks of platelet response" and "consistent platelet response" and used them to derive a comparable treatment difference of the drugs versus placebo.

The company's approach is not appropriate. The 302 and 305 studies are irrelevant for the assessment of added benefit of avatrombopag.

Likewise, the data presented by the company in the form of a network metaanalysis and the comparison of data from the pivotal studies are unsuitable for assessing any added benefit. There is no mention in Module 4 B of the dossier that any studies for the network metaanalyses or for the comparison of studies have been identified on the basis of systematic literature searches. No systematic data analysis of any kind is discernible. Information is missing on the study pool of the network metaanalysis, and no information whatsoever is available on the characteristics of the included studies. For the outcomes on platelet counts, the company submitted results selectively. The data presented by the company are unsuitable for the benefit assessment of avatrombopag in comparison with the ACT.

Results on added benefit

In its dossier, the company did not submit any suitable data for assessing any added benefit of avatrombopag in adult patients with primary chronic ITP who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) in comparison with the ACT specified by the G-BA. Consequently, there is no hint of added benefit of avatrombopag in comparison with the ACT; an added benefit is therefore not proven.

2.4 Probability and extent of added benefit

Table 5 presents a summary of the results regarding the benefit assessment of avatrombopag in comparison with the ACT.

Table 5: Avatrombopag – probability and extent of added benefit

Indication	**ACT**[a]	**Probability and extent of added benefit**
Treatment of primary chronic ITP in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)[b]	Eltrombopag or romiplostim	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. For this indication, patients are assumed to require medical treatment and to be refractory mainly to corticosteroids.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; ITP: immunothrombocytopaenia

The assessment described above deviates from that by the company, which derived a hint of non-quantifiable added benefit.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a21-32.html.