IQWiG Reports – Commission No. A20-53

Fostamatinib (chronic immune thrombocytopenia) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Fostamatinib (chronische Immunthrombozytopenie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 September 2020). 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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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. 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
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITP	immune thrombocytopenia
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
WHO	World Health Organization

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 fostamatinib. 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 26 June 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of the present report is the assessment of the added benefit of fostamatinib in comparison with eltrombopag or romiplostim as appropriate comparator therapy (ACT) in adult patients with chronic immune thrombocytopenia (ITP), who are refractory to other treatments.

The research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of fostamatinib

Research question	Therapeutic indication	ACT[a]
1	Treatment of chronic ITP in adult patients who are refractory to other treatments[b]	Eltrombopag or romiplostim

a. Presentation of the respective ACT specified by the G-BA.
b. For the present therapeutic indication, it is assumed that patients were in need of medical treatment and that these patients were mostly refractory to corticosteroids.

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

The company named eltrombopag and romiplostim as ACT and thus followed the options 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 concurs with the company's inclusion criteria.

Results

In its dossier, the company presented no suitable data for the assessment of the added benefit of fostamatinib. The placebo-controlled studies conducted by the company do not enable a

comparison versus the ACT. This resulted in no hint of an added benefit of fostamatinib versus the ACT; an added benefit is therefore not proven.

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

Based on the results presented, probability and extent of the added benefit of the drug fostamatinib in comparison with the ACT are assessed as follows:

Table 3 shows a summary of probability and extent of the added benefit of fostamatinib.

Table 3: Fostamatinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Treatment of chronic ITP in adult patients who are refractory to other treatments[b]	Eltrombopag or romiplostim	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. For the present therapeutic indication, it is assumed that patients were in need of medical treatment and that these patients were mostly refractory to corticosteroids.

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

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 the present report is the assessment of the added benefit of fostamatinib in comparison with eltrombopag or romiplostim as ACT in adult patients with chronic ITP, who are refractory to other treatments.

The research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of fostamatinib

Research question	Therapeutic indication	ACT[a]
1	Treatment of chronic ITP in adult patients who are refractory to other treatments[b]	Eltrombopag or romiplostim

a. Presentation of the respective ACT specified by the G-BA.

b. For the present therapeutic indication, it is assumed that patients were in need of medical treatment and that these patients were mostly refractory to corticosteroids.

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

The company named eltrombopag and romiplostim as ACT and thus followed the options 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 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 of the company in the dossier:

- study lists on fostamatinib (status: 4 May 2020)
- bibliographical literature search on fostamatinib (last search on 6 May 2020)
- search in trial registries/trial results databases for studies on fostamatinib (last search on 6 May 2020)
- search on the G-BA website for fostamatinib (last search on 6 May 2020)
- bibliographical literature search on ACTs (last search on 6 May 2020)
- search in trial registries/trial results databases for studies on ACTs (last search on 19 June 2020)
- search for ACTs on the GBA website (last search on 4 May 2020)

To check the completeness of the study pool:

- search in trial registries for studies on fostamatinib (last search on 6 July 2020)

Concurring with the company, the check of the study pool identified no RCTs that would allow a direct comparison versus the ACT. Due to the lack of directly comparative data, the company explored the possibility of an adjusted indirect comparison via the common comparator "placebo". For the ACT, the company identified no studies suitable for an indirect comparison.

In its dossier, the company presented the two placebo-controlled studies 047 [3] and 048 [3] and used them to derive the added benefit. The company presented the single-arm extension study 049 [4] as supplementary information. The approach of the company was inadequate since the ACT of the G-BA was not implemented in the studies. The company's studies are described below.

Studies 047 and 048 presented by the company

Die RCTs 047 and 048 were planned and conducted identically. Both RCTs were double-blind, multicentre approval studies on the comparison of fostamatinib with placebo in adults with persistent or chronic ITP, who had to have received at least one pretreatment.

To be included in the study, the patients had to have an average platelet count < 30 x 10^9/L and no value > 1 in any localisation of the ITP bleeding scale during a 4-week screening phase. After completion of the screening phase, 76 (study 047) and 74 (study 048) patients were included and randomly assigned to fostamatinib or placebo in a 2:1 ratio stratified by splenectomy (yes vs. no) and platelet count (< 15 × 10^9/L vs. ≥ 15 × 10^9/L). At baseline, more than 90% of the patients included had chronic ITP by definition (> 12 months since diagnosis).

Treatment with fostamatinib was in compliance with the Summary of Product Characteristics (SPC) [5]. Patients in the control arm received an identical treatment regimen with placebo. Corticosteroids at an equivalent dose of < 20 mg prednisone per day, azathioprine or danazol were allowed as concomitant medication. Immunoglobulins and corticosteroids could be administered as rescue medication.

The primary outcome of the studies 047 and 048 was defined as stable platelet response at week 24 (≥ 50 x 10^9/L in at least 4 of 6 visits in weeks 14 – 24). Further outcomes were mortality, frequency and severity of bleeding, use of rescue medication and adverse events (AEs).

The treatment phase was 24 weeks, followed by 2 weeks of follow-up observation. Subsequently, patients could continue treatment with fostamatinib in extension study 049.

The company presented the results of 047 and 048 separately and as meta-analysis.

Due to the missing implementation of the ACT alone, the studies 047 and 048 provide no data suitable for the derivation of an added benefit. Moreover, it cannot be inferred from the

available documentation whether the patient populations in studies 047 and 048 adequately reflect the approved therapeutic indication of fostamatinib. Overall, about 94% of the patients were pretreated with corticosteroids. However, about 40% of the patients in the intervention arm and about 60% in the control arm continued to receive concomitant treatment with corticosteroids during the 24-week treatment phase. It is therefore questionable whether these patients were refractory to other types of treatment, especially corticosteroids, according to the approved therapeutic indication.

Moreover, it remains unclear whether the patients had diseases requiring treatment. According to the guideline of the German Society for Hematology and Medical Oncology, treatment of chronic ITP is only mandatory in cases of severe bleeding [6]. At baseline, the patients included showed no relevant bleeding symptoms (World Health Organization [WHO] mean bleeding grade approx. 0.55). About half of the patients received no drug treatment at baseline. It is therefore questionable whether drug intervention was required for these patients at the time the study started.

Study 049

Study 049 is an open-label, multicentre, single-arm extension study. In order to participate in study 049, patients had to have completed study 047 or 048 or had to have terminated the study prematurely due to ineffectiveness. The patients in the study were treated with fostamatinib. The study included a total of 123 patients with persistent or chronic ITP.

Study 049 presented by the company as supplementary information was unsuitable for the derivation of an added benefit, because being a single-arm study it permitted no comparison with the ACT.

2.4 Results on added benefit

In its dossier, the company presented no suitable data for the assessment of the added benefit of fostamatinib. This resulted in no hint of an added benefit of fostamatinib versus the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

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

Table 5: Fostamatinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Treatment of chronic ITP in adult patients who are refractory to other treatments[b]	Eltrombopag or romiplostim	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. b. For the present therapeutic indication, it is assumed that patients were in need of medical treatment and that these patients were mostly refractory to corticosteroids. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; ITP: immune thrombocytopenia		

The assessment described above deviates from that of the company, which derived an indication of minor added benefit of fostamatinib.

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/a20-53.html.