Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Fostamatinib (Chronic Immune Thrombocytopenia)

of 17 December 2020

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out based on evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient fostamatinib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 July 2020. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 26 June 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 October 2020, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of fostamatinib compared with the appropriate comparator therapy could be determined based on the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the written statements made in the written and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit based on their therapeutic relevance (qualitative) according to the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in

accordance with the General Methods [1] was not set aside in the benefit assessment of fostamatinib.

In the light of the above and taking into account the written statements received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of fostamatinib (Tavlesse) in accordance with the product information

Tavlesse is indicated for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments.

Therapeutic indication of the resolution (resolution of 17 December 2020):

See therapeutic indication according to marketing authorisation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with chronic immune thrombocytopenia who are refractory to other treatments

Appropriate comparator therapy for fostamatinib:

Eltrombopag or romiplostim

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

[1] General Methods, Version 6.0 dated 5 November 2020. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. In the therapeutic indication, the following medicinal products are approved for the treatment of primary immune thrombocytopenia in adult patients: dexamethasone, prednisolone, methylprednisolone, prednisone, immunoglobulins, human platelet concentrate, eltrombopag, romiplostim, and azathioprine.

On 2. For the treatment of chronic immune thrombocytopenia, splenectomy may be considered as a non-medicinal therapy.

On 3. in the aforementioned therapeutic indication, there are no resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V or of non-medicinal treatments.

On 4. The general state of medical knowledge was illustrated by systematic research for guidelines and reviews of clinical studies in the indication thrombocytopenia (ITP) and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

In this regard, it should be noted that the reliable evidence on therapy options in the present therapeutic indication is limited overall.

There are two systematic reviews that assess the efficacy and safety profile of the thrombopoietin receptor agonists (TRA) eltrombopag and romiplostim in the treatment of immune thrombocytopenia. Eltrombopag and romiplostim show comparable efficacy and safety profiles. Another review examines the efficacy of the combination regimen of rituximab and dexamethasone compared with the monotherapy of dexamethasone. Rituximab is not approved for the treatment of immune thrombocytopenia (off-label use).

There is no higher-quality evidence for the efficacy and safety of splenectomy. Overall, splenectomy is considered only in exceptional cases and is therefore not included in the appropriate comparator therapy.

In accordance with the product information, a therapy with immunoglobulin (IVIg) or platelet concentrate is mainly indicated in patients with a high risk of bleeding or before operations or in emergencies in patients with severe thrombocytopenia. It is thus assumed that such therapy with IVIg or platelet concentrate is not regularly indicated for continuous treatment of chronic immune thrombocytopenia.

In clinical practice, the treatment of ITP is essentially based on the clinical bleeding tendency and the platelet count. Other individual factors (e.g. stage of disease, previous course of disease, comorbidities, concomitant medication) also play a role that must be taken into account when deciding on therapy. Depending on the above criteria, either a "monitoring wait-and-see approach" or medicinal therapy mainly with corticosteroids is recommended in first-line therapy for mild disease expression. As second-line therapy, treatment with TRA is recommended for patients requiring therapy.

Even if some patients with ITP manage without permanent therapy, it is assumed that there is a need for medical treatment in the patients in the present therapeutic indication. It is also assumed that the patients in the present therapeutic indication are mainly refractory to corticosteroids.

In accordance with the information in the European Public Assessment Report[2] on fostamatinib by the European Medicines Agency (EMA), the sub-group of secondary immune thrombocytopenia accounts for only 20% of ITP diagnoses. However, this sub-group is not part of the indication of fostamatinib targeted in the approval process. In addition, according to the inclusion criteria of pivotal studies 047 and 048, only patients with a diagnosis of ITP for at least 3 months and no known cause of thrombocytopoenia

[2] European Public Assessment Report (EPAR) on Tavlesse dated 14 November 2019: EMA/CHMP/654949/2019 https://www.ema.europa.eu/en/documents/assessment-report/tavlesse-epar-public-assessment-report_en.pdf *[accessed 20 November 2020]*

were treated with fostamatinib. In accordance with the exclusion criteria, patients with thrombocytopoenia associated with myeloid dysplasia, autoimmune haemolytic anaemia, or another disease such as chronic lymphocytic leukaemia, viral infection, autoimmune disease, thyroid disease, or induced or alloimmune thrombocytopoenia were excluded from the studies. Against this background and because no data are available for fostamatinib in the treatment of secondary ITP, the G-BA assumes that, in principle, patients with primary chronic ITP represent the target population in the therapeutic indication of fostamatinib. It is therefore not considered necessary to determine an appropriate comparator therapy for the therapeutic indication of secondary ITP.

Based on the evidence available and taking into account the recommendations from clinical practice, the G-BA assumes that in the present therapeutic indication for the treatment of chronic ITP in adult patients who are refractory to other types of treatment, the vast majority of patients to be treated are mainly refractory to corticosteroids. Thus, eltrombopag or romiplostim is determined as the appropriate comparator therapy. This is also supported by the pivotal studies in which most patients were pre-treated with corticosteroids.

However, taking into account the bleeding tendency, symptomatology, comorbidities, and, in particular, a possible previous therapy with eltrombopag and romiplostim, it cannot be ruled out that in certain patients in the present therapeutic indication, a comprehensive treatment by (continued) administration of TRA can no longer be considered a regular option.In clinical practice, the active ingredients rituximab, azathioprine, ciclosporin, cyclophosphamide, and mycophenolate mofetil are used as possible therapy options for the treatment of these patients. However, except for azathioprine, the aforementioned active ingredients are not approved. There is thus a discrepancy between medicinal products approved in the indication and those used in care. Even after reviewing the available evidence according to the generally recognised state of medical knowledge, no evidence can be found for a benefit in the treatment of chronic immune thrombocytopenia by the aforementioned active ingredients, including azathioprine. Overall, the G-BA considers it appropriate to refrain from a separate determination of the appropriate comparator therapy for those patients who are refractory to TRA.

In summary, eltrombopag or romiplostim is determined as the appropriate comparator therapy.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment contract.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of fostamatinib is assessed as follows:

Adult patients with chronic immune thrombocytopenia who are refractory to other treatments

An additional benefit is not proven.

Justification:

Randomised controlled trials 047 and 048 were submitted for the assessment of the additional benefit of fostamatinib compared with the appropriate comparator therapy. Both studies were double-blind, multi-centre pivotal studies with identical study designs evaluating fostamatinib compared with placebo in adult patients with persistent or chronic immune thrombocytopenia who were expected to have received at least one pre-treatment.

The study included patients who, among other things, had an average platelet count of < 30 × 10^9/l and who were not found to have a value > 1 in any localisation according to the ITP bleeding scale. A total of 76 (Study 047) and 74 (Study 048) patients were included and stratified by splenectomy (yes vs no) and platelet count (< 15 × 10^9/l vs. ≥ 15 × 10^9/l). Study participants were randomised to a fostamatinib or placebo arm at a ratio of 2:1. At the start of study, more than 90% of the patients included had chronic ITP by definition (> 12 months since diagnosis).

In addition to the study medication (fostamatinib or placebo), therapy with corticosteroids (corresponding to < 20 mg prednisone/day), azathioprine, or danazol was allowed as concomitant medication in both arms provided that their dose had been constant for at least 14 days before baseline. This dose was not allowed to change during the duration of the study. All other therapies for ITP that the patients may have received as pre-treatment before the start of study were discontinued in accordance with the study protocol (taking into account washout periods) and were therefore no longer permitted as concomitant therapies during the course of the study.

Overall, 94% of patients were pre-treated with corticosteroids upon study inclusion. In the further course of the study, however, approx. 40% of patients in the intervention arm and approx. 60% in the control arm continued to receive concomitant therapy with corticosteroids during the 24-week treatment phase.

Based on the data available, it cannot be conclusively assessed to what extent or to which other therapies for the treatment of ITP (apart from corticosteroids) the patients were refractory.

The primary endpoint of both studies was defined as stable platelet response at Week 24 (≥ 50 × 10^9/l on at least 4 of 6 rounds at Weeks 14–24). Other endpoints were mortality, frequency and severity of bleeding, use of rescue medication, and adverse events (AE).

The treatment phase was 24 weeks, followed by 2 weeks of follow-up. The patients were then able to continue treatment with fostamatinib in extension study 049.

Because the placebo-controlled studies presented did not compare fostamatinib with the specific appropriate comparator therapy, these studies are not suitable for early benefit assessment. The supplementary open-label, multi-centre, single-arm extension study 049, in which all patients were treated with fostamatinib, is also ineligible.

In summary, based on the studies presented, no statements can be made regarding the additional benefit of fostamatinib compared with the appropriate comparator therapy. Because of the lack of implementation of the appropriate comparator therapy, an assessment of the additional benefit is not possible.

2.1.4 Summary of the assessment

The present assessment refers to the benefit assessment of the new medicinal product Tavlesse with the active ingredient fostamatinib.

Fostamatinib is approved for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments.

In the therapeutic indication to be considered, the following patient group was defined:

Adult patients with chronic immune thrombocytopenia who are refractory to other treatments

The G-BA determined the appropriate comparator therapy for the aforementioned patient group:

Eltrombopag or romiplostim.

According to the information provided in the European Public Assessment Report on fostamatinib by the European Medicines Agency (EMA) and in accordance with the study population of the pivotal studies, the G-BA assumes that, in principle, patients with primary chronic ITP represent the target population in the therapeutic indication of fostamatinib.

The double-blind, randomised, controlled pivotal studies 047 and 048 were presented. These investigated the treatment of fostamatinib compared with placebo in adult patients with predominantly chronic immune thrombocytopenia who had received at least one pre-treatment.

Because the placebo-controlled studies presented did not compare fostamatinib with the specific appropriate comparator therapy, these studies are not suitable for early benefit assessment.

In summary, based on the studies presented, no statements can be made regarding the additional benefit of fostamatinib compared with the appropriate comparator therapy. Because of the lack of implementation of the appropriate comparator therapy, an assessment of the additional benefit is not possible.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA bases its resolution on the patient numbers provided by the pharmaceutical company in the dossier. However, these are subject to uncertainties. Overall, the figure is assessed as overestimated because it also includes patients who do not show the resistance to other forms of treatment required in the therapeutic indication.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Tavlesse (active ingredient: fostamatinib) at the following publicly accessible link (last access: 10 November 2020):
https://www.ema.europa.eu/en/documents/product-information/tavlesse-epar-product-information_de.pdf

Treatment with fostamatinib should be started and monitored throughout by doctors experienced in the treatment of haematological diseases.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 December 2020).

Treatment duration:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is different for each individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Fostamatinib	continuously, 2 × daily	365	1	365
Appropriate comparator therapy				
Eltrombopag	continuously, 1 × daily; if necessary, every second day	182.5–365	1	182.5–365
Romiplostim	continuously, every 7 days	52.1	1	52.1

Usage and consumption:

The active ingredient romiplostim is dosed depending on body weight. For the calculation of the dosages as a function of body weight, the average body measurements from the official representative statistics “Microcensus 2017– Questions about Health – body measurements of the population” were used as a basis (average body weight): 77.0 kg).[3]

The minimum dosage of eltrombopag is 12.5 mg once a day or, alternatively, 25 mg every other day in accordance with the product information. The dosage of 12.5 mg once daily cannot be achieved with the potencies on the market at the time of the Lauer referred to.

Because it is not always possible to achieve the exact calculated dose per day with the commercially available potencies, in these cases, the dose is rounded up or down to the next higher or lower dose available.

[3] Statistisches Bundesamt [German Federal Office for statistics]. (2018). Mikrozensus 2017 - Fragen zur Gesundheit - Körpermaße der Bevölkerung [Microcensus 2017 – Questions about health – Body measurements of the population]. https://www.destatis.de/DE/Methoden/Qualitaet/Qualitaetsberichte/Bevoelkerung/mikrozensus-2017.pdf;jsessionid=B922CBC0E7D233E5ACE6BA7FAD0CC37A.internet8731?__blob=publicationFile (access: 15 October 2020).

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Fostamatinib	100–150 mg	200 – 300 mg	2 × 100 mg – 2 × 150 mg	365	730 × 100 mg – 730 × 150 mg
Appropriate comparator therapy					
Eltrombopag	12.5 mg – 75 mg	12.5 mg – 75 mg	1 × 25 mg – 1 × 75 mg	182.5–365	182.5 × 25 mg – 365 × 75 mg
Romiplostim	1 × 1 µg/kg = 77 µg – 1 × 10 µg/kg = 770 µg	77–770 µg	1 × 125 µg – 1 × (500 + 250 + 125) µg	52.1	52.1 × 125 µg – 52.1 × (500 + 250 + 125) µg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates according to Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Fostamatinib 100 mg	60 FCT	€ 4,476.70	€ 1.77	€ 259.00	€ 4,215.93
Fostamatinib 150 mg	60 FCT	€ 6,687.08	€ 1.77	€ 388.50	€ 6,296.81
Appropriate comparator therapy					
Eltrombopag 25 mg	84 FCT	€ 4,085.51	€ 1.77	€ 385.10	€ 3,698.64

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Eltrombopag 75 mg	84 FCT	€ 12,144.68	€ 1.77	€ 1,155.32	€ 10,987.59
Romiplostim 125 µg	1 PIJ	€ 588.09	€ 1.77	€ 156.34	€ 429.98
Romiplostim 250 µg	4 PIJ	€ 3,254.11	€ 1.77	€ 187.37	€ 3,064.97
Romiplostim 500 µg	4 PIJ	€ 6,451.80	€ 1.77	€ 374.72	€ 6,075.31
Abbreviations: FCT: film-coated tablets; PSI: powder and solvent for solution for injection; PLJ: powder for the preparation of an injection solution					

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 1 December 2020

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be assessed and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 23 July 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. At its session on 7 January 2020, the Subcommittee on Medicinal Products redefined the appropriate comparator therapy.

On 26 June 2020, the pharmaceutical company submitted a dossier for the benefit assessment of fostamatinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 26 June 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient fostamatinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 September 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 1 October 2020. The deadline for submitting written statements was 22 October 2020.

The oral hearing was held on 9 November 2020.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 8 December 2020, and the proposed resolution was approved.

At its session on 17 December 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	23 July 2019	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	7 January 2020	Redefinition of the appropriate comparator therapy
Working group Section 35a	4 November 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	9 November 2020	Conduct of the oral hearing
Working group Section 35a	18 November 2020 2 December 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	8 December 2020	Concluding discussion of the draft resolution
Plenum	17 December 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 17 December 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken