Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V: Avatrombopag (immune thrombocytopenia)

of 16 September 2021

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 on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies 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 benefits,
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. Costs of therapy for the statutory health insurance,
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 (German) market of the active ingredient avatrombopag 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 April 2021. 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 22 March 2021.

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 July 2021, thus initiating the written statement procedure. In addition, an oral hearing was also held.

The G-BA came to a resolution on whether an additional benefit of avatrombopag compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with 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 used in the benefit assessment of avatrombopag.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has come to 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 avatrombopag (Doptelet®) in accordance with the product information

Doptelet is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure.

Doptelet is indicated for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

Therapeutic indication of the resolution (resolution from 16.09.2021):

Doptelet is indicated for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with primary chronic immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)

- 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 in accordance with 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 a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.
4. Comparative therapy should be part of the appropriate therapy in the therapeutic indication according to the generally accepted state of medical knowledge.

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

on 1. The following medicinal products are approved for the present therapeutic indication besides avatrombopag: dexamethasone, prednisolone, methylprednisolone, prednisone, immunoglobulins, human platelet concentrate, eltrombopag, romiplostim, azathioprine, and fostamatinib.

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

on 3. The following resolutions or guidelines of the G-BA are available for the present therapeutic indication:
   - Fostamatinib – resolution of 17 December 2020

on 4. The general state of medical knowledge was illustrated by a systematic search for guidelines and reviews of clinical studies in the therapeutic indication primary immune

thrombocytopenia and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to § 35a SGB V".

In clinical practice, immune thrombocytopenia (ITP) treatment is mainly based on the clinical bleeding tendency and the platelet count. In addition, other individual factors (e.g. stage of the disease, previous course of the disease, comorbidities, concomitant medication) play a role that must be taken into account when deciding on treatment. Even if some patients with ITP manage without permanent therapy, it is assumed that the patients in the present therapeutic indication have a need for medical treatment.

According to the product information, the therapy with immunoglobulin (IVIg) or platelet concentrate is mainly indicated in patients with a high risk of bleeding or before operations or in emergency cases in patients with severe thrombocytopenia, so that it is assumed that such therapy with IVIg or platelet concentrate is not regularly indicated for continuous treatment of chronic ITP.

Overall, the robust evidence on therapeutic options in the present therapeutic indication is limited. Five systematic reviews and two guidelines are available.

There is no superior evidence for the efficacy and safety of splenectomy. According to the current state of medical knowledge, this form of therapy is not included in the appropriate comparator therapy.

One review examines the efficacy of dexamethasone vs prednisolone, and another review examines the efficacy of combination treatment of rituximab and dexamethasone compared to monotherapy with dexamethasone. Rituximab is not approved for the treatment of ITP (off-label use).

Three reviews evaluate the efficacy and safety profile of eltrombopag and romiplostim in the treatment of chronic ITP. Eltrombopag and romiplostim show comparable efficacy and safety profiles. The Neunert et al, 2019[2] and Provan et al., 2019[3] guidelines recommend eltrombopag and romiplostim for treating chronic ITP in adults that are refractory to other therapies.

In January 2020, the active ingredient fostamatinib was approved to treat chronic immune thrombocytopenia (ITP) in adults who are refractory to other types of treatment. By resolution of the G-BA of 17 December 2020, it was determined that an additional benefit of fostamatinib compared to the appropriate comparator therapy was not proven, as no comparison of fostamatinib versus the specific appropriate comparator therapy (eltrombopag or romiplostim) was conducted in the submitted

2 Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv 2019;3(23):3829-3866.

3 Provan D, Arnold DM, Bussel JB, Chong BH, Cooper N, Gernsheimer T, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv 2019;3(22):3780-3817.

placebo-controlled studies. Fostamatinib is therefore not an appropriate comparator therapy.

Based on the available evidence 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 adults who are refractory to other types of treatment, the vast majority of patients to be treated are mainly refractory to corticosteroids. However, it cannot be ruled out that in certain subjects in the present therapeutic indication, taking into account the bleeding tendency, bleeding symptomatology, comorbidities and in particular a possible previous therapy with eltrombopag and romiplostim, a comprehensive therapy through the (continued) administration of thrombopoietin receptor agonists (TRA) is no longer regularly an option. In clinical practice, the active ingredients rituximab, azathioprine, ciclosporin, cyclophosphamide, mycophenolate mofetil are used as possible therapeutic options for the treatment of these patients. However, except for azathioprine, the above-mentioned active ingredients are not approved (off-label use). Therefore, there is a discrepancy between medicinal products approved in the indication and medicinal products used in health 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 ITP by the above-mentioned active ingredient, 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 treatment-resistant to TRA.

In summary, based on the available evidence and taking into account the above, the equally appropriate therapeutic options of eltrombopag or romiplostim are determined as the appropriate comparator therapies for adults with primary chronic immune thrombocytopenia (ITP) who do not respond to other therapies (e.g. corticosteroids, immunoglobulins).

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

2.1.3 Extent and probability of the additional benefit

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

An additional benefit is not proven.

Justification:

The pharmaceutical company does not identify any relevant studies for the assessment of the additional benefit of avatrombopag compared to the appropriate comparator therapy. He nevertheless submits Study 302 and Study 305. In addition, the pharmaceutical company describes an independent network meta-analysis as well as a comparison of the data from the pivotal studies for avatrombopag, eltrombopag and romiplostim.

Study 302

Study 302 is a randomised, double-blind Phase III study comparing avatrombopag versus placebo in patients with ITP who have received at least one prior therapy. The previous therapies were not limited to corticosteroids and immunoglobulins. Included patients had to have also a mean baseline platelet count of < 30 x 10^9/l. Patients were randomised in a 2:1 ratio to the study arms (N=32 avatrombopag, N=17 placebo). In addition to the study medication, concomitant medication with corticosteroids, azathioprine, mycophenolate mofetil (MMF), danazol and ciclosporin A was allowed in both study arms.

The study was conducted in 27 centres in Europe, Oceania, Asia and Africa between February 2012 and April 2015. A randomised study duration of 26 weeks was planned. The primary endpoint in Study 302 was defined as the cumulative number of weeks with platelet response. In addition, further endpoints on morbidity (e.g. incidence and severity of bleeding events), health-related quality of life, side effects and mortality were recorded.

Because the placebo-controlled study presented did not compare avatrombopag to the specific appropriate comparator therapy for which it was intended, Study 302 is not suitable for evaluating the additional benefit of avatrombopag.

Study 305

The supplemental Study 305 is a double-blind, randomised phase III study comparing avatrombopag versus eltrombopag in adult patients with pretreated primary chronic ITP. Adults had to have received at least one prior ITP therapy that was not limited to corticosteroids or immunoglobulins. Study duration of six months was planned. The pharmaceutical company does not provide detailed information on the study design and the study population in the dossier.

Study 305 had to be discontinued prematurely due to recruitment problems and thus does not meet the minimum study duration of 24 weeks considered necessary for chronic diseases. Study 305 is therefore not suitable for assessing the additional benefit of avatrombopag compared with the appropriate comparator therapy.

Network meta-analysis and comparison of data from pivotal studies of avatrombopag, eltrombopag, and romiplostim

The results of the network meta-analysis presented by the pharmaceutical company as well as the comparison of the data from the pivotal studies on avatrombopag, eltrombopag and romiplostim, are not suitable for the assessment of the additional benefit of avatrombopag. It is not shown that the studies for the network meta-analysis or the comparison of studies were identified based on systematic literature searches. There is no systematic processing of the data. Furthermore, in addition to the information on the study pool of the network meta-analysis, any information on the characteristics of the included studies is missing. Furthermore, only selective results for endpoints on platelet counts are available.

In summary, on the basis of the studies presented and further analyses, no conclusions can be drawn regarding the additional benefit of avatrombopag compared with the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Doptelet®" with the active ingredient avatrombopag. The active ingredient avatrombopag is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure and primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). The therapeutic indication assessed here is as follows: Adult patients with primary chronic immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

The G-BA determined eltrombopag and romiplostim as the appropriate comparator therapy. For the present therapeutic indication, the pharmaceutical company presents the phase III studies Study 302 and Study 305 as well as further analyses.

Study 302 compares avatrombopag versus placebo. As study 302 did not compare avatrombopag versus the specific appropriate comparator therapy, the study is not suitable for the assessment of the additional benefit.

Study 305 compares avatrombopag versus eltrombopag. The study had to be discontinued prematurely due to recruitment problems and does not meet the minimum study duration of 24 weeks considered necessary for chronic diseases. The data of the study are not suitable for the assessment of the additional benefit.

The other analyses (network meta-analysis, comparison of data from individual studies) are not suitable for the assessment of the additional benefit due to substantial methodological deficiencies and selective endpoint presentation.

In summary, no conclusions can be drawn regarding the additional benefit of avatrombopag based on the data presented. An additional benefit of avatrombopag compared to the appropriate comparator therapy is therefore not proven.

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).

However, the G-BA bases its resolution on the patient numbers provided in the pharmaceutical company's dossier, which are subject to uncertainties.

The upper limit of patient numbers is considered to be overestimated. When calculating the number of patients, the pharmaceutical company does not take into account that, according to the therapeutic indication of avatrombopag, adults do not respond to other therapies. For example, adults whose disease responds to corticosteroids are not excluded from the target population. In addition, the percentages used for treatment-naive adults may include patients who have undergone treatment and subsequently achieved remission, as well as patients who are not eligible for sustained treatment. For the assumption of an upper limit of 75% of treatment-naive adults, based on the publication by Depré et al. (2018),[4] patients who were included in the evaluation over a 20-year period and received treatment during their observation phase were considered. This does not take into account that in ITP, all lines of therapy allow for observation phases without therapy, making adults ineligible for avatrombopag at this time. The therapy-free periods are not sufficiently included in the percentage extraction, so it can only be transferred to the previous calculation steps to a limited extent.

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 Doptelet (active ingredient: avatrombopag) at the following publicly accessible link (last access: 11 June 2021):

https://www.ema.europa.eu/en/documents/product-information/doptelet-epar-product-information_en.pdf

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

[4] Depré F, Aboud N, Mayer B et al. Efficacy and tolerability of old and new drugs used in the treatment of immune thrombocytopenia: Results from a long-term observation in clinical practice. PLoS One 2018; 13(6): e0198184.

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 September 2021).

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 patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/patient or patent/year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

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

Designation of the therapy	Treatment mode	Number of treatments/patient or patient//year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Avatrombopag	continuously, 1 x daily, if necessary, 1 – 3 x every 7 days	52.1 - 365	1	52.1 - 365
Appropriate comparator therapy				
Eltrombopag	continuously, 1 x daily, if necessary, every 2 days	182.5 - 365	1	182.5 - 365
Romiplostim	Continuously, every 7 days	52.1	1	52.1

Consumption:

The active ingredient romiplostim is dosed depending on body weight. For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg).[5]

The minimum dosage of eltrombopag is 12.5 mg once daily or, alternatively, 25 mg every other day, according to 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's last revision. Therefore, the presentation of the alternative dosage of 25 mg is done every other day.

[5] Statistisches Bundesamt (Federal Statistic Office). (2018). Microcensus 2017 - Questions on health- body measurements of the population https://www.destatis.de/DE/Methoden/Qualitaet/Qualitaetsberichte/Bevoelkerung/mikrozensus-2017.pdf;jsessionid=B922CBC0E7D233E5ACE6BA7FAD0CC37A.internet8731?__blob=publicationFile

Designation of the therapy	Dosage/ application	Dose/ patient/ or patient/ treatment days	Usage by potency/ day of treatment	Treatment days/ Patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Avatrombopag	20 mg – 40 mg	20 mg – 40 mg	1 x 20 mg – 2 x 20 mg	52.1 - 365	52.1 x 20 mg – 730 x 20 mg
Appropriate comparator therapy					
Eltrombopag	25 mg – 75 mg	25 mg – 75 mg	1 x 25 mg – 1 x 75 mg	182.5 - 365	182.5 x 25 mg – 365 x 75 mg
Romiplostim	1 x 1 µg/kg = 77 µg – 1 x 10 µg/kg = 770 µg	77 µg – 770 µg	1 x 125 µg – 1 x (500 + 250 + 125) µg	52.1	52,1 x 125 µg – 52,1 x (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 in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. The required number of packs of a particular potency was first determined based on consumption to calculate the annual treatment costs. 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 doses of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

Costs of the medicinal products:

Designation of the therapy	Packaging 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					
Avatrombopag 20 mg	30 FCT	€ 3,690.71	€ 1.77	€ 207.50	€ 3,481.44
Appropriate comparator therapy					
Eltrombopag 25 mg	84 FCT	€ 4,191.17	€ 1.77	€ 370.17	€ 3,819.23
Eltrombopag 75 mg	84 FCT	€ 12,458.76	€ 1.77	€ 1,110.50	€ 11,346.49
Romiplostim 125 µg	1 PSI	€ 606.25	€ 1.77	€ 157.12	€ 447.36
Romiplostim 250 µg	4 PSI	€ 3,354.67	€ 1.77	€ 188.31	€ 3,164.59
Romiplostim 500 µg	4 PSI	€ 6,651.46	€ 1.77	€ 376.59	€ 6,273.10
Abbreviations: FCT = film-coated tablets, PSI = powder for solution for injection					

LAUER-TAXE® last revised: 1 September 2021

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 evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be considered 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 use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

Other SHI benefits: not applicable

3. Bureaucratic costs calculation

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 21 April 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 22 March 2021, the pharmaceutical company submitted a dossier for the benefit assessment of avatrombopag to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 1 VerfO.

By letter dated 22 March 2021, 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 avatrombopag.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 June 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 July 2021. The deadline for submitting written statements was 22 July 2021.

The oral hearing was held on 9 August 2021.

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 the 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 7 September 2021, and the proposed resolution was approved.

At its session on 16 September 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Sub-committee Medicinal product	21 April 2020	Determination of the appropriate comparator therapy
Working group Section 35a	4 August 2021	Information on statements received; preparation of the oral hearing
Sub-committee Medicinal product	9 August 2021	Conduct of the oral hearing
Working group Section 35a	18 August 2021 1 September 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Sub-committee Medicinal product	7 September 2021	Final discussion of the draft resolution
Plenum	16 September 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 September 2021

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken