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 (thrombocytopenia with chronic liver disease)

of 16 September 2021

Contents

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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.

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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 with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by 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 severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure.

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

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2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with severe thrombocytopenia with chronic liver disease who are scheduled to undergo an invasive procedure

- Monitoring wait-and-see approach

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: Administration of platelet concentrates, lusutrombopag. Lusutrombopag is not placed on the German market.

on 2. A non-medicinal treatment paid by the SHI is not considered as an appropriate comparator therapy in the present therapeutic indication.

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

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

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

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

Patients with thrombocytopenia due to chronic liver disease are usually indicated conservatively for planned invasive medical procedures because of the increased risk of bleeding. In these cases, the clinical assessment of the risk of bleeding is then made preoperatively, taking into account the general clinical condition of the subject and the thrombocytopenia.

The only therapeutic option besides avatrombopag approved and available in Germany in the therapeutic indication is platelet transfusion ("for the treatment of a bleeding tendency caused by severe thrombocytopenia due to thrombotic bleeding disorders, in an emergency also in the case of metabolic disorders, but not in the case of a low platelet count alone").

In the present therapeutic indication, the decision for a platelet transfusion can be made both as prophylaxis and for acute treatment during planned invasive procedures according to the doctor's instructions.

Overall, the evidence for the administration of platelet concentrates is very limited, and the recommendations that can be derived are not clear: Thus, for the present therapeutic indication, the European Association for the Study of the Liver guideline (2018)[2] does not explicitly recommend treatment for thrombocytopenia in general or specifically before surgical procedures. Based on indirect evidence, the National Institute for Health and Care Excellence (NICE) guideline (2015)[3] recommends the use of platelet transfusion in patients with thrombocytopenia in the presence of clinically significant bleeding. According to the NICE guideline and the American Association of Blood Banks guideline (2015)[4], prophylactic use of platelet transfusion could be considered for subjects with thrombocytopenia undergoing a planned invasive procedure. In contrast, the American Association for the Study of Liver Diseases guideline (2020)[5] recommends patient-individual assessment in the presence of severe thrombocytopenia due to a lack of evidence for the regular use of prophylactic platelet transfusions.

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2 European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69(2):406-460.

3 National Clinical Guideline Centre. Blood transfusion [online]. London (GBR): National Institute for Health and Care Excellence; 2015. [Accessed: 11.02.2020]. (NICE Guideline; Volume 24).

4 Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, et al. Platelet transfusion: a clinical practice guideline from the AABB. Ann Intern Med 2015;162(3):205-213.

5 Northup PG, Garcia-Pagan JC, Garcia-Tsao G et al. Vascular Liver Disorders, Portal Vein Thrombosis, and Procedural Bleeding in Patients With Liver Disease: 2020 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2021; 73(1): 366-413.

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The scientific literature does not provide a clear threshold of platelet counts in the blood for the use of platelet transfusion depending on a specific invasive procedure. Platelet values cited in guidelines for the use of platelet transfusions range from < 100 000/µl to < 20 000/µl depending on the extent of the invasive procedure. Furthermore, according to the current state of medical knowledge, no standardised criteria can be derived according to which the need for transfusion of patients is assessed. Among other things, the type and method of the invasive procedure, the type of anaesthesia planned, the extent of resection, the possibility of local haemostasis, plasmatic coagulation, type and stage of liver disease, comorbidities such as renal insufficiency, concomitant medications (especially anticoagulation) as well as other accompanying co-factors play a role.

Overall, the available evidence shows that the use of platelet transfusions in the present therapeutic indication may be indicated mainly as a prophylactic measure with a certain lead time to surgery, but also as an acute patient-individual treatment of significant bleeding, but does not represent a regular therapeutic option that is used for all patients.

Therefore, in the present therapeutic indication, the "monitoring wait-and-see approach" is determined as the appropriate comparator therapy, whereby platelet transfusions may be indicated patient-individual in the context of the appropriate comparator therapy. In the context of a clinical study, platelet transfusions may be indicated as needed in both study arms.

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:

For the benefit assessment, the pharmaceutical company submits a meta-analysis of the data of the completed, double-blind, randomised ADAPT-1 and ADAPT-2 studies.

The ADAPT-1 and ADAPT-2 studies have an identical study design. The studies compared avatrombopag versus placebo. Adults with chronic liver disease of various aetiologies and severe thrombocytopenia (defined as platelet count < 50 x 10^9/l) were included. In addition, subjects had to be scheduled for an invasive procedure, and a platelet transfusion based on medical assessment had to be indicated to reduce the risk of bleeding associated with the procedure unless there was a clinically significant increase in platelet levels compared with baseline. The studies were conducted between 2014 and 2017 in 75 and 74 centres in the Americas, Europe, Australia, and Asia.

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Patients in the studies were on average 56 and 58 years old, respectively, and had a median baseline platelet count of approximately 38 x 10^9/l. Over 80% of subjects had a MELD score of ≤ 14 and a Child-Turcotte-Pugh (CTP) stage A or B. The most common cause of the chronic liver disease was chronic hepatitis C. Subjects with a Model for End-stage Liver Disease (MELD) score of > 24 were not included in the ADAPT-1 and ADAPT-2 studies.

A total of 231 subjects were randomised in the ADAPT-1 study and 204 subjects in the ADAPT-2 in a 1:2 ratio to the two study arms (ADAPT-1: N= 149 avatrombopag and N= 82 placebo; ADAPT-2: N= 128 avatrombopag and N= 76 placebo). Randomisation was stratified by low (<40 x 10^9/l) or higher baseline platelet count (≥40 to <50 x 10^9/l), presence of hepatocellular carcinoma (HCC), and bleeding risk associated with the planned procedure (low, intermediate, high). The treatment was carried out in accordance with the information provided in the avatrombopag product information. In both study arms, there was the option to perform a prophylactic and/or acute platelet transfusion according to the assessment of the principal investigator. In this regard, platelet levels were determined at each visit, and the number and timing of platelet transfusions were documented. Due to bleeding, other concomitant medications or rescue procedures were allowed under restrictions but were performed in only 2 subjects in the ADAPT-2 study.

A total of 14 types of invasive procedures were allowed in the studies, which included gastrointestinal endoscopy with or without planned biopsy, alcohol ablation or chemoembolisation for hepatocellular carcinoma (HCC), biliary interventions, dental procedures, and others. The assessment of the associated risk of bleeding was made according to the consensus guideline of Malloy et al.[6] and the assessment of clinical experts. A maximum of 60% was planned for procedures with a low risk of bleeding. Invasive procedures were performed five to eight days after completion of 5 days of treatment with avatrombopag or placebo. The follow-up period included two visits and ended a maximum of 35 days after randomisation.

Based on the available evidence and taking into account the statements of the scientific-medical societies concerning the written statement procedure, no uniform criteria for assessing the bleeding risk of patients can be derived. On the one hand, the categorisation of invasive procedures according to low, moderate, and high bleeding risk differs between the various guidelines or recommendations. On the other hand, when assessing the bleeding risk of patients, not only the type and method of the invasive procedure play a role, but also numerous other factors such as the type of anaesthetic procedure planned, the extent of resection, the possibility of local haemostasis, plasmatic coagulation, type and stage of liver disease, comorbidities such as renal insufficiency, concomitant medication (especially anticoagulation) as well as other accompanying co-factors. Based on these considerations, separate consideration of patient populations undergoing interventions with low or intermediate and high-risk bleeding risk is not undertaken.

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[6] Malloy PC, Grassi CJ, Kundu S et al. Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. J Vasc Interv Radiol 2009; 20(7 Suppl): S240-249.

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Extent and probability of the additional benefit

Mortality

Deaths were recorded in the ADAPT-1 and ADAPT-2 studies as part of the adverse event assessment.

In the meta-analyses of the studies, no statistically significant difference was detected between the treatment groups. An additional benefit of avatrombopag for the endpoint mortality is therefore not proven.

Morbidity

Patients without transfusion

The primary endpoint of the ADAPT-1 and ADAPT-2 studies was the percentage of patients who did not require platelet transfusions or rescue procedures due to bleeding after randomisation up to 7 days after a scheduled procedure.

When looking at the overall population of the ADAPT-1 and ADAPT-2 studies, there is a statistically significant difference in favour of avatrombopag.

Based on the available patient characteristics and the nature of the planned interventions in the ADAPT-1 and ADAPT-2 studies, it is not clear alone that prophylactic platelet transfusion was indicated in the patients included in the studies. Especially for interventions with a low risk of bleeding, guidelines tend to set lower platelet thresholds or recommend that prophylactic platelet transfusion be avoided. According to the inclusion criteria of the ADAPT-1 and ADAPT-2 studies, patients had to be indicated for platelet transfusion to reduce the risk of bleeding associated with the procedure, based on medical assessment. However, documentation of the doctor's decision regarding the patient's need for transfusion did not occur in the ADAPT-1 and ADAPT-2 studies. Thus, to what extent prophylactic platelet transfusions were indicated for the included patients in the ADAPT-1 and ADAPT-2 studies cannot be assessed.

During the written statement procedure, it was discussed that platelet transfusions might be associated with relevant secondary complications (e.g. alloimmunisation, bacterial and viral infections, transfusion-related pulmonary oedema (TRALI)). The risk for transfusion-related secondary complications increases especially when platelet transfusions are performed regularly. However, the present therapeutic indication refers to the treatment of thrombocytopenia prior to a planned invasive procedure. Against this background, the probability of the occurrence of transfusion-related complications is considered to be low. In addition, it was discussed that an alloimmunisation would be relevant, especially for patients in whom liver transplantation is to be performed subsequently due to the possible favouring of a rejection reaction. Reliable data on the level of risk for the occurrence of alloimmunisation or for the promotion of a rejection reaction after liver transplantation have not been presented.

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In the present studies, there was no statistically significant difference in patient-relevant endpoints in the categories of morbidity and/or side effects with regard to the potential prevention of acute secondary complications of platelet transfusion. Given the limited follow-up duration of the ADAPT-1 and ADAPT-2 studies, no conclusions can be drawn regarding the potential prevention of longer-term transfusion-related sequelae.

Overall, taking into account the aspects described, no additional benefit is derived from the results of the endpoint "patients without transfusion".

Bleeding WHO grade ≥ 2

For the endpoint bleeding with WHO grade ≥ 2, the meta-analysis of the studies showed no statistically significant difference between the study arms.

An additional benefit of avatrombopag for the endpoint bleeding with WHO grade ≥ 2 is therefore not proven.

Quality of life

Data on health-related quality of life were not collected in the. ADAPT-1 and ADAPT-2 studies.

Side effects

Adverse events occurred in > 50% of patients in the ADAPT-1 study and in > 40% of patients in the ADAPT-2 study arms. The results for the endpoint "Adverse events are only presented additionally.

There were no statistically significant differences between the treatment groups for the endpoints serious adverse events (SAE) and discontinuation due to AEs. For the endpoint discontinuation due to AEs, no event occurred in the ADAPT-2 study.

There was no statistically significant difference between the study arms of the ADAPT-2 study for the endpoint thromboembolic events. No event for this endpoint occurred in the ADAPT-1 study.

Overall assessment / conclusion

To assess the additional benefit of avatrombopag, the pharmaceutical company submitted a meta-analysis of the double-blind, randomised phase III studies ADAPT-1 and ADAPT-2 comparing avatrombopag versus placebo with results on mortality, morbidity and side effects.

However, there were no statistically significant differences in the meta-analysis regarding overall survival.

In the endpoint category morbidity, results are available for the endpoints "patients without transfusion" and "bleeding with WHO grade ≥ 2".

There was no statistically significant difference in the meta-analysis for the endpoint Bleeding with WHO grade ≥ 2. An additional benefit of avatrombopag for this endpoint is therefore not proven.

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Based on the results of the endpoint "patients without transfusion", no additional benefit is derived.

For the endpoints serious adverse events (SAE), discontinuation due to AEs and thromboembolic events, there was no statistically significant effect of avatrombopag. Therefore, an additional benefit of avatrombopag compared with the monitoring wait-and-see approach in the endpoint category side effects is not proven.

In summary, an additional benefit of avatrombopag over the monitoring wait-and-see approach is not proven.

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: Adults with severe thrombocytopenia with chronic liver disease who are scheduled to undergo an invasive procedure.

The G-BA determined the "monitoring wait-and-see approach" as the appropriate comparator therapy, whereby platelet transfusions may also be indicated on a patient-individual basis within the context of the appropriate comparator therapy. In the context of a clinical study, platelet transfusions may be indicated as needed in both study arms.

The pharmaceutical company presents a meta-analytical evaluation of the data of phase III ADAPT-1 and ADAPT-2 studies, in which avatrombopag is compared against placebo. An assessment of the health-related quality of life did not take place in the studies.

There was no statistically significant difference for the endpoint mortality and for the morbidity endpoint bleeding with WHO grade ≥ 2.

Based on the results of the endpoint "patients without transfusion", no additional benefit is derived.

There are no statistically significant differences between the study arms for the endpoints serious adverse events (SAE), discontinuation due to AEs and thromboembolic events.

Overall, an additional benefit of avatrombopag 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).

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

The wide range of the target population is based solely on a reported range on percentages of severe thrombocytopenia, the upper range of which tends to be classified as an overestimate. There is uncertainty as to the extent to which the diagnostic group used and the corresponding ICD code allow sufficient derivation of the number of adults with severe thrombocytopenia and chronic liver disease. In addition, the number of adults with cirrhosis in 2021 is subject to uncertainty because it was obtained by extrapolation using linear regression with a low value at the coefficient of determination. The percentages of the studies used for severe thrombocytopenia are largely subject to uncertainty due to the consideration of selected populations or data from individual hospitals. Overall, the number of patients is more likely to be at the lower end of the range.

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.

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:

The present therapeutic indication of avatrombopag relates to the treatment of severe thrombocytopenia in adults with chronic liver disease who are scheduled for an invasive procedure. The number of treatments per patient per year can therefore vary patient-individual depending on the number of planned invasive procedures in a year. The present calculation is based on one to three invasive procedures per year.

The performance of prophylactic platelet transfusions to reduce the bleeding risk of patients, as well as the use of platelet transfusions for the treatment of acute bleeding during or after invasive surgery, represents a measure in the present therapeutic indication which may be indicated on a patient-individual basis within the scope of the appropriate comparator

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therapy. Since both the type of invasive procedure and the associated risk of bleeding as well as the number of invasive procedures performed per year may differ depending on the patient, the costs of the appropriate comparator therapy are patient-individual different.

Platelet transfusions may also be indicated in addition to avatrombopag.

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[7]	1 x daily	1 - 3	5	5 - 15
Appropriate comparator therapy				
Monitoring wait-and-see approach	patient-individual[8]			

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ or patient/ treatment days	Usage by potency/ day of treatment	Treatment days/ Patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Avatrombopag	40 mg – 60 mg	40 mg – 60 mg	2 x 20 mg – 3 x 20 mg	5 - 15	10 x 20 mg – 45 x 20 mg
Appropriate comparator therapy					
Monitoring wait-and-see approach	Patient-individual[8]				

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

[7] Platelet transfusions may be indicated in addition to avatrombopag.
[8] Platelet transfusions may be indicated patient-individual as part of the appropriate comparator therapy.

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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[7]	10 FCT	€ 1,260.32	€ 1.77	€ 69.17	€ 1,189.38
Avatrombopag 20 mg[7]	15 FCT	€ 1,874.05	€ 1.77	€ 103.75	€ 1,768.53
Appropriate comparator therapy					
Monitoring wait-and-see approach	Patient-individual[8]				
Abbreviations: FCT = film-coated tablets					

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

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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 24 March 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 01 July 2021. The deadline for submitting written statements was 22 July 2021.

The oral hearing was held on 9 August 2021.

By letter dated 10 August 2021, the IQWiG was commissioned with a supplementary assessment. The addenda prepared by IQWiG was submitted to the G-BA on 27 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 was 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.

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Chronological course of consultation

Session	Date	Subject of consultation
Sub-committee Medicinal product	24 March 2020	Determination of the appropriate comparator therapy
Working group Section 35a	3 August 2021	Information on statements received; preparation of the oral hearing
Sub-committee Medicinal product	9 August 2021 10 August 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
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

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