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
Lusutrombopag (thrombocytopenia with chronic liver disease)

of 19 May 2022

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 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 the 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 is 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 lusutrombopag 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 December 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 30 November 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 March 2022, 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 lusutrombopag 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 lusutrombopag.

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 Lusutrombopag (Mulpleo) in accordance with the product information

Mulpleo is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures.

Therapeutic indication of the resolution (resolution of 19 May 2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with severe thrombocytopenia due to chronic liver disease who are scheduled to undergo invasive procedures

Appropriate comparator therapy for lusutrombopag:

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.

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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 products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA 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.

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 lusutrombopag: Human platelet concentrate, avatrombopag.

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. The following resolutions and guidelines of the G-BA exist regarding medicinal treatments in the present therapeutic indication:

Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

Avatrombopag: Resolution of 16 September 2021

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

In addition to lusutrombopag, the thrombopoietin receptor agonist avatrombopag is approved in Germany for the treatment of adults with severe thrombocytopenia due to liver disease who are scheduled for invasive procedure. For avatrombopag, the resolution of 16 September 2021 stated that the additional benefit compared to the monitoring wait-and-see approach is not proven. Against this background, avatrombopag is not considered to be an appropriate comparator therapy.

Furthermore, platelet transfusions are approved in the indication ("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 prevention 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.

The scientific literature does not provide a clear threshold value 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 a resection, the possibility of local haemostasis, plasmatic coagulation, type and stage of liver disease, comorbidities such as renal failure, 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.

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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: 21.02.2022]. (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-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.

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 lusutrombopag 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 from the completed, double-blind, randomised studies M0626, L-PLUS 1 and L-PLUS 2 comparing lusutrombopag with placebo.

The studies included adults with chronic liver disease of various aetiologies and severe thrombocytopenia (defined as a platelet count < 50 x 10^9/l) and a Child-Pugh score of A or B. Patients included in the studies had to have an invasive procedure planned.

M0626

The M0626 study was conducted in 63 study sites in Japan between August 2012 and April 2013. Only adults who were scheduled to undergo percutaneous ablation of the liver due to hepatocellular carcinoma as an invasive procedure were included.

Patients in the studies were on average 69 years old, and had a median baseline platelet count of approximately 42 x 10^9/l. 58 % of the subjects had a Child-Pugh score of A. The most common cause of chronic liver disease was chronic hepatitis C.

In study M0626, a total of 61 patients were randomised to a total of 4 study arms: Lusutrombopag 3 mg (N=16); lusutrombopag 2 mg (N=15), lusutrombopag 4 mg (N=15) and placebo (N=15). Only the results of patients who received 3 mg lusutrombopag were used for the benefit assessment.

Randomisation was stratified by baseline platelet count (< 35 x 10^9/l vs ≥ 35 x 10^9/l to < 45 x 10^9/l vs ≥ 45 x 10^9/l) and Child-Pugh score (A vs. B).

L-PLUS 1

The L-PLUS 1 study was conducted in 81 study sites in Japan between October 2013 and May 2014.

The procedures performed in the study included liver procedures (radiofrequency ablation, transarterial chemoembolisation) and gastrointestinal procedures (endoscopic variceal ligation, endoscopic injection sclerotherapy). Procedures not permitted included

laparotomies, thoracotomies and craniotomies. Patients in the studies were on average 68 years old, and had a median baseline platelet count of approximately 40 x 10^9/l. Half of the patients each had a Child-Pugh score of A or B. The most common cause of chronic liver disease was chronic hepatitis C.

A total of 97 subjects were randomised in a 1:1 ratio to the two study arms (N= 49 lusutrombopag; N= 48 placebo). Randomisation was stratified by baseline platelet count (< 35 x 10^9/l vs ≥ 35 x 10^9 /l to < 45 x 10^9/l vs ≥ 45 x 10^9/l) and planned invasive procedure (liver ablation/coagulation vs other).

L-PLUS 2

The multinational L-PLUS 2 study was conducted from July 2015 to April 2017 in 138 study sites in America, Europe, Australia and Asia. The L-PLUS 2 study included subjects who were scheduled for an invasive procedure that was likely to require a platelet transfusion. The same specifications regarding the excluded invasive procedures existed as in the L-PLUS 1 study.

Patients in the studies were on average 56 years old, and had a median baseline platelet count of approximately 38 x 10^9/l. 63 % of the subjects had a Child-Pugh score of A. The most common cause of chronic liver disease was chronic hepatitis C.

A total of 215 subjects were randomised in a 1:1 ratio to the two study arms (N= 108 lusutrombopag; N= 107 placebo). Randomisation was stratified by baseline platelet count (< 35 x 10^9/l vs ≥ 35 x 10^9/l) and planned invasive procedure (liver ablation/coagulation vs other).

On the interventions implemented in the studies

The treatment of patients with lusutrombopag was carried out according to the requirements in the product information. The invasive procedures were performed on day 9 - 14 after the 7-day treatment with lusutrombopag or placebo. The follow-up period was 28 days and ended a maximum of 35 days after randomisation.

In all three studies, there was the option to perform prophylactic and/or acute platelet transfusions according to the principal investigator's assessment in both study arms, although the specifications differed between the studies. The need for platelet transfusion prior to invasive surgery was determined by the platelet count determined preoperatively (≤ 2 days prior to invasive surgery). In the L-PLUS 2 study, prophylactic platelet transfusions were prescribed for platelet counts< 50 x 10^9/l, whereas in the L-PLUS 1 and M0626 studies platelet transfusions were allowed for platelet counts below this value. Furthermore, platelet transfusions were possible in the context of emergency measures due to acute bleeding. Further concomitant medication or rescue procedures due to bleeding were permitted under restrictions, but were only carried out in one subject in study L-PLUS 2 and one subject in study L-PLUS 1.

The number and timing of platelet transfusions were documented. The risk of bleeding associated with the invasive procedure was not documented in the L-PLUS 2, L-PLUS 1 and M0626 studies. The assessment of bleeding risk depends on a variety of different factors (e.g. type and method of invasive procedure, type of planned anaesthetic procedure, extent of resection, possibility of local haemostasis, plasmatic coagulation, type and stage of liver

disease, comorbidities such as renal failure, concomitant medications (especially anticoagulation)) and, as a result, is not categorised uniformly between the different guidelines or recommendations. 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 the assessment of the bleeding risk of patients can be derived.

Extent and probability of the additional benefit

Mortality

For the endpoint overall mortality, there was no statistically significant difference between the treatment groups in the L-PLUS 2 study. No subject died in the studies L-PLUS 1 and M0626.

Morbidity

Patients without transfusion

The primary endpoint of the L-PLUS 2 study was the percentage of patients who did not require platelet transfusions before the invasive procedure nor emergency measures due to bleeding after randomisation and up to 7 days after the procedure. The primary endpoint of the L-PLUS 1 and M0626 studies was the percentage of patients who did not receive platelet transfusions prior to invasive surgery. When looking at the results for the endpoint "patients without transfusion", there is a statistically significant difference in favour of lusutrombopag in the studies L-PLUS 2, L-PLUS 1 and M0626.
The available patient characteristics and the nature of the planned interventions of the studies L-PLUS 2, L-PLUS 1 and M0626 alone do not indicate 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 should be avoided. Also, during the oral hearing on the benefit assessment of lusutrombopag, the German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS) explained that a general indication for the performance of a prophylactic platelet transfusion during invasive procedures with a low risk of bleeding is usually not given even if a platelet value of $< 50 \times 10^9$/l is present.
According to the inclusion criteria of the L-PLUS 2, L-PLUS 1 and M0626 studies, patients had to have an initial platelet count of $< 50 \times 10^9$/l at the time of screening. The medical decision on preoperative platelet administration was based on the platelet value at the time ≤ 2 days before the invasive procedure, whereby a prophylactic platelet transfusion was prescribed in the L-PLUS 2 study at platelet values of $< 50 \times 10^9$/l and permitted in the L-PLUS 1 and M0626 studies above this threshold.

An evaluation of the other reasons for the medical decision regarding the patients' need for transfusion in the L-PLUS 2, L-PLUS 1 and M0626 studies was not provided. Thus, it cannot be assessed to what extent prophylactic platelet transfusions were indicated for the included patients in the L-PLUS 2, L-PLUS 1 and M0626 studies.

In the context of the present written statement procedure on the benefit assessment of lusutrombopag and the written statement procedure on avatrombopag (resolution of 16 September 2021), it was discussed that platelet transfusions can 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 secondary complications are considered to be low. In addition, an alloimmunisation would be relevant especially for patients in whom a 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.
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 L-PLUS 2, L-PLUS 1 and M0626 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 L-PLUS 2 study showed no statistically significant difference between study arms. In the L-PLUS 1 and M0626 studies, serious bleeding occurred in one subject each, but bleeding events were not recorded according to WHO severity classification. An additional benefit of lusutrombopag 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 L-PLUS 2, L-PLUS 1 and M0626 studies.

Side effects

Adverse events occurred in > 40% of patients in the study arms in study L-PLUS 2, in > 90% in study L-PLUS 1 and in 100% in study M0626. The results for the endpoint "Adverse events" are only presented additionally. For the endpoint of serious adverse events (SAE), the meta-analysis of the three studies shows no significant difference between the study arms. For the endpoint discontinuation due to AEs, there is no significant difference between the study arms in the L-PLUS 2 study. No events related to this endpoint occurred in the L-PLUS 1 and M0626 studies. For the endpoint thromboembolic events, there was no statistically significant difference in the meta-analysis of the three studies.

Overall assessment / conclusion

For the assessment of the additional benefit of lusutrombopag, the pharmaceutical company submitted a meta-analysis of the double-blind, randomised L-PLUS 2, L-PLUS 1 and M0626 studies comparing lusutrombopag versus placebo with results on mortality, morbidity and side effects.

There is no statistically significant difference for the 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 for the endpoint "bleeding with WHO grade ≥ 2". An additional benefit of lusutrombopag for this endpoint is therefore not proven.

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 difference between lusutrombopag and placebo. An additional benefit of lusutrombopag compared with the monitoring wait-and-see approach in the endpoint category side effects is therefore not proven.

In summary, an additional benefit of lusutrombopag 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 "Mulpleo" with the active ingredient lusutrombopag. The active ingredient lusutrombopag is used to treat severe thrombocytopenia in adults with chronic liver disease who are undergoing invasive surgery.

The G-BA determined "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 the L-PLUS 2, L-PLUS 1 and M0626 studies, in which lusutrombopag is compared against placebo. An assessment of 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.

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

Overall, an additional benefit of lusutrombopag 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).

The G-BA based its resolution on the patient numbers determined in the resolution on the benefit assessment of the active ingredient avatrombopag for the treatment of severe thrombocytopenia in adults with chronic liver disease who are scheduled for invasive procedure (resolution of 16 September 2021). These are subject to uncertainties due to the following aspects:

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 a 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.

The uncertainties with regard to the diagnostic group used and the corresponding ICD codes as well as with regard to the range shown also apply to the patient numbers calculated in the present benefit assessment procedure for lusutrombopag. In the opinion of the G-BA, the patient numbers presented here therefore do not represent a clearly better estimate compared to the patient numbers from the previous resolution on avatrombopag.

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 Mulpleo (active ingredient: lusutrombopag) is freely available at the following link:

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

(last access: 12 May 2022)

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 May 2022).

Treatment period:

The present therapeutic indication of lusutrombopag relates to the treatment of severe thrombocytopenia in adults with chronic liver disease who have to undergo invasive procedures. 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[6].

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 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 lusutrombopag.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Lusutrombopag[7]	1 x daily	1 - 3	7	7 - 21
Appropriate comparator therapy				
Monitoring wait-and-see approach	Different from patient to patient[8]			

[6] EPAR Doptelet (avatrombopag): https://www.ema.europa.eu/en/documents/assessment-report/doptelet-epar-public-assessment-report_en.pdf (last accessed: 12 April 2022).

[7] Platelet transfusions may be indicated in addition to lusutrombopag.

[8] Platelet transfusions may be indicated patient-individual as part of the appropriate comparator therapy.

Consumption:

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					
Lusutrombopag[7]	3 mg	3 mg	1 x 3 mg	7 - 21	7 x 3 mg – 21 x 3 mg
Appropriate comparator therapy					
Monitoring wait-and-see approach	Different from patient to patient[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 Section 130 and Section 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. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of 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 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					
Lusutrombopag 3 mg[7]	7 FCT	€ 1,528.46 €	€ 1.77	€ 84.00	€ 1,442.69
Appropriate comparator therapy					
Monitoring wait-and-see approach	Different from patient to patient[8]				
Abbreviations: FCT = film-coated tablet					

LAUER-TAXE® last revised: 1 May 2022

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 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 the 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.

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 6 November 2018, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 30 November 2021, the pharmaceutical company submitted a dossier for the benefit assessment of lusutrombopag to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 30 November 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 lusutrombopag.

The dossier assessment by the IQWiG was submitted to the G-BA on 25 February 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 March 2022. The deadline for submitting written statements was 22 March 2022.

The oral hearing was held on 11 April 2022.

On 14 April 2022, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 1.1 dated 14 April 2022 replaces version 1.0 of the dossier assessment dated 25 February 2022. The assessment result was not affected by the changes in version 1.1 compared to version 1.0.

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 was discussed at the session of the subcommittee on 10 May 2022, and the proposed resolution was approved.

At its session on 19 May 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	6 November 2018	Determination of the appropriate comparator therapy
Working group Section 35a	6 April 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	11 April 2022	Conduct of the oral hearing
Working group Section 35a	21 April 2022 4 May 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	10 May 2022	Concluding discussion of the draft resolution
Plenum	19 May 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 19 May 2022

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

Prof. Hecken