Justification

Gemeinsamer Bundesausschuss

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

of 20 February 2020

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved in accordance with Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999, according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, Nos. 2 and 3 SGB V in conjunction with Chapter 5, Sections 5 et seq. of the Rules of Procedure, G-BA (VerfO) has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT, exceeds € 50 million during the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the

G-BA, submit evidence in accordance with Chapter 5, Section 5, paragraphs 1 – 6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5, Section 6 VerfO and prove the additional benefit compared with the appropriate comparator therapy.

In accordance with Section 35a paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered be proven through the grant of marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit provided is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (*cf*. Section 35a paragraph 1 sentence 12 SGB V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

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

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient volanesorsen in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 1 of the Rules of Procedure of the G-BA (VerfO) is 15 August 2019. 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 28 June 2019.

Volanesorsen as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999.

According to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed by the G-BA on the basis of the approval studies.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published together with the IQWiG assessment on the website of the G-BA (www.g-ba.de) on 15 November 2019, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G19-13) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1 numbers 1 through 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of volanesorsen.

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

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of volanesorsen (Waylivra®) in accordance with the product information

Waylivra is indicated as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome
(FCS) and at high risk for pancreatitis, in whom response
to diet and triglyceride lowering therapy has been inadequate.

2.1.2 Extent of the additional benefit indicating the significance of the evidence

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

1 General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

For adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate, there is a hint for a non-quantifiable additional benefit for volanesorsen because the scientific data basis does not allow quantification.

Justification:

For the benefit assessment, the pharmaceutical company presents the results of the pivotal, randomised, blinded, placebo-controlled APPROACH Phase III study, which is the basis for marketing authorisation as well as supplementary results of the randomised, blinded, placebo-controlled COMPASS Phase III study and the open-label, single-arm, long-term APPROACH OLE study.

In the APPROACH study 67 patients with familial chylomicronemia syndrome were randomised 1:1 to the volanesorsen arm or the placebo arm and stratified according to a history of pancreatitis (yes/no) as well as the intake of fibrates and/or medically prescribed omega-3 fatty acids (yes/no). One person randomised to the placebo arm discontinued treatment before the first trial medication. After an eight-week screening phase (run-in phase), the patients received subcutaneous volanesorsen or placebo once a week for 52 weeks. At the end of the study round at week 52, the study participants entered either a follow-up phase of 13 weeks or the extension study APPROACH OLE.

The primary objective of this study was to evaluate the efficacy of volanesorsen compared with placebo in terms of the percentage change in fasting triglyceride levels from baseline to month 3. Secondary and exploratory endpoints included abdominal pain, confirmed acute pancreatitis, quality of life, and side effects.

The study was conducted in the USA, Spain, the United Kingdom, Canada, France, Italy, Germany, Israel, Brazil, Hungary, the Netherlands, and South Africa in August 2014 and March 2017.

In the COMPASS study, patients with severe hypertriglyceridaemia (N = 114) were investigated. The study does not contain any information relevant for the benefit assessment beyond that of the APPROACH study because less than 10% of the patients (N = 7) had FCS in accordance with the present therapeutic indication and because the treatment duration is significantly shorter (26 weeks). The results of the COMPASS study are therefore not considered for the benefit assessment.

In the open-label, uncontrolled APPROACH OLE study, therapy experienced and therapy naïve patients from the APPROACH and COMPASS studies as well as therapy naïve FCS patients not included in the APPROACH and COMPASS studies were treated with volanesorsen for 52 weeks. At the end of the treatment period, study participants were able to participate in an Expanded Access Program or maintain the dosage for another 52 weeks until an appropriate program was approved and started in the respective country. Patients who did not participate in such a program switched to a follow-up phase with a duration of 13 weeks.

According to the inclusion criteria, patients from the APPROACH and COMPASS studies were able to switch to APPROACH OLE only if they had completed the studies with an acceptable safety profile (assessed by sponsor and medical investigators). It is therefore questionable whether the results of the study could be transferred to everyday clinical care. Because this is an uncontrolled study, no comparative statements on efficacy and safety can be derived. A high risk of bias at the study and endpoint level can therefore be assumed. Because of the uncertainties mentioned, the results of the APPROACH OLE study are not considered for the benefit assessment.

Mortality

In the APPROACH study, deaths were recorded as safety events. No deaths occurred during the study.

No statements on the extent of the additional benefit can be derived from the data on mortality.

Morbidity

Change in fasting triglyceride values

In the present therapeutic indication, the triglyceride levels in the blood is a clinically relevant parameter, which is used for diagnosis and therapy control. The therapeutic goal in the treatment of FCS is the reduction of triglyceride levels in the blood in order to reduce the risk of acute pancreatitis, among other things. However, the symptomatology of patients with FCS is different for each individual patient, and there is limited evidence for symptom-relevant blood triglyceride levels. Beyond that, no valid data could be identified to show what effect a certain change in triglyceride levels in FCS patients has on patient-individual symptomatology or on the risk of acute pancreatitis.

For the endpoint change in the percentage of fasting triglyceride, there is a statistically significant difference in favour of volanesorsen compared with placebo after a treatment duration of 3, 6, and 12 months. The fasting triglyceride value decreases by 59.6% after 12 months after treatment with volanesorsen and by 2.7% after treatment with placebo (median difference: −47.8 [95% CI -69.2; -26.4]; p value < 0.0001).

Abdominal pain

Abdominal pain was recorded using an electronic patient diary. It was surveyed on a weekly basis whether abdominal pain occurred within the last week and if so, what the maximum intensity of pain was on an 11-point NRS from 0 (no pain) to 10 (unbearable pain). For the point value of 5, the attribute “moderate pain” is specified in the patient diary. The baseline value was defined as the average of the maximum intensity during the screening and week 1 of the study. Abdominal pain was also summarised according to the following categories: none (pain value: 0), mild (pain value: 1–3), moderate (pain value: 4–6) or strong (pain value: 7–10).

In the volanesorsen arm, 42.4% of the study participants discontinued the treatment phase prematurely; in the placebo arm, only 5.9% of the patients. There are no data available on the recording of abdominal pain after discontinuation of treatment. From week 26 onwards, the calculated return rate in the volanesorsen arm fell well below 70%; in the placebo arm, a rate of over 70% was achieved by the end of study. The data collected therefore do not allow valid statements regarding abdominal pain in the entire study population. The data for the endpoint “abdominal pain” are therefore not presented in the benefit assessment.

Frequency of independently confirmed acute pancreatitis

Pancreatitis is a relevant and stressful complication of FCS. The endpoint is therefore not considered patient relevant.

Acute pancreatitis has been confirmed by a blinded, independent Pancreatitis Adjudication Committee (PAC) based on pre-specified criteria. Independently confirmed acute pancreatitis was “Documented pancreatitis” based on the Revised Atlanta Diagnostic Criteria for acute

pancreatitis. “Probable pancreatitis” and “Possible pancreatitis” were based on different criteria.

During the treatment and follow-up phase, independently confirmed pancreatitis occurred in one patient in the volanesorsen arm and three patients in the placebo arm. Because of differences in the median treatment duration in the 52-week treatment phase between the treatment groups (346 days in the volanesorsen arm and 358 days in the placebo arm), the calculated effect estimator, not adjusted for the treatment time, is strongly biased and is not shown.

Frequency of the combination of episodes of acute pancreatitis and/or patient-reported abdominal pain

For the combined endpoint, the combination of the annual rate of acute pancreatitis and/or patient-reported moderate or severe abdominal pain (pain score: 4–10) during the treatment period was calculated.

The restrictions regarding the return rate for the endpoint “abdominal pain” of less than 70% in the volanesorsen arm in the second half of the treatment phase also apply to the combined endpoint. Therefore, the results of the combined endpoint are also not presented in the benefit assessment.

Change in health status using the EQ-5D-VAS

The EQ-5D-VAS is a scale from 0 to 100 on which patients assess their health status. A value of 0 corresponds to the worst conceivable health status and a value of 100 to the best conceivable health status. Because the return rate at weeks 26 and 52 is below 70% in both study arms, only the data for week 13 are presented in the benefit assessment. However, data were not available from all patients at baseline (volanesorsen arm: 72.7%; placebo arm: 78.8%).

At week 13, there was no statistically significant difference between the treatment arms.

No statements on the extent of the additional benefit can be derived from the data on morbidity.

<u>Quality of life</u>

Change in quality of life using the SF-36

The SF-36 is a cross-disease measuring instrument for recording health-related quality of life. It consists of eight domains with a total of 35 items. The different domains are additionally combined into a physical (PCS) and a mental (MCS) component score. PCS includes the domain scales for physical functioning, physical role function, physical pain and general health perception. The MCS incorporates the domain scales of vitality, social functioning, emotional role function, and mental well-being. Values from 0 to 100 can be assumed, whereby a higher value reflects a better health status.
As with the EQ-5D-VAS, not all patient data is available for the SF-36 at baseline (volanesorsen arm: 72.7%; placebo arm: 78.8%). Because the return rate at weeks 26 and 52 is also below 70% in both study arms, only the data for week 13 are presented in the benefit assessment.

In the individual domains as well as the physical (PCS) and mental (MCS) component score, there is no statistically significant difference between the treatment arms at week 13.

No statements on the extent of the additional benefit can be derived from the data on quality of life.

Side effects

The results of a *post hoc* sensitivity analysis conducted by the pharmaceutical company were used to present the overall rates of side effects. In this analysis, the endpoints abdominal pain and acute pancreatitis, which were already recorded as patient-relevant endpoints in the morbidity category, were excluded.

During the treatment and follow-up phase, an AE occurred in almost all patients in both the volanesorsen and placebo arms (97.0 and 90.9%, respectively). However, an AE that led to therapy discontinuation occurred only in the volanesorsen arm in nine individuals (27.3%). Severe adverse events occurred in 5 (15.2%) patients in the volanesorsen arm and in 1 (3.0%) patients in the control arm. Serious adverse events in 6 (18.2%) patients in the volanesorsen arm and in 2 (6.1%) patients in the control arm. Furthermore, there are sometimes differences between the study arms with regard to the number of patients with certain AE. Skin and subcutaneous tissue disorders, and blood and lymphatic system disorders occurred in 54.5% and 30.3% of patients in the volanesorsen arm and in 18.2% and 6.1% of patients in the placebo arm. A decrease in thrombocyte count occurred in 11 patients (33.3%) in the volanesorsen arm and in one patient (3%) in the placebo arm; thrombocytopenia occurred only in four patients (12.1%) in the volanesorsen arm.

Bleeding events occurring as AE are also summarised under the adverse event of special interest (AESI) “bleeding” defined *a priori*. In the marketing authorisation process, the survey of AESIs regularly serves to identify special risks of the medicinal product to be assessed. They therefore represent a further approach to the category side effects based on PTs. This can provide additional information based on typical risks of the active ingredient or typical risks in the therapeutic indication. Because in the present resolution all SOCs and PTs according to MedDRA are already represented with a uniform cut-off and minimum difference between the arms, the AESI bleeding is at least partly a different, summarised representation of the same bleeding events.

Bleeding occurred in 16 (48.5%) patients in the volanesorsen arm and in 4 (12.1%) patients in the control arm.

The pharmaceutical company does not provide suitable effect estimator to assess the safety endpoints that take into account the different treatment duration in the two study arms (median therapy duration (min, max) of 346 days (57, 372) in the volanesorsen arm and 358 days (163, 379) in the placebo arm). The results on side effects are therefore potentially biased in favour of volanesorsen because of the shorter treatment duration in the volanesorsen arm. For this reason, the data on side effects cannot be conclusively assessed.

No statements on the extent of the additional benefit can be derived from the data on side effects.

Overall assessment

As an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate, results on mortality, morbidity, quality of life, and side effects are available based on the APPROACH pivotal study.
No statements on the extent of the additional benefit can be derived from the data on mortality.

In the morbidity category, a statistically significant difference in favour of volanesorsen compared with placebo after a treatment duration of 3, 6, and 12 months was shown for the primary endpoint “change in the percentage of fasting triglyceride levels”. In the present therapeutic indication, the triglyceride levels in the blood is a clinically relevant parameter, which is used for diagnosis and therapy control. Beyond that, however, no valid data could be identified to show what effect a certain change in triglyceride levels in FCS patients has

on patient-individual symptomatology or on the risk of acute pancreatitis. No statements on the extent of the additional benefit can be derived from the data on morbidity.

Nor can any statements on the extent of the additional benefit be derived from the data on quality of life and side effects.

In summary, the present results are classified as non-quantifiable in their extent because the scientific data basis does not allow quantification.

Significance of the evidence

For the benefit assessment, the results of the randomised, blinded, placebo-controlled Phase III APPROACH study will be considered. The results of the study are subject to uncertainties.

Within the study, more patients in the volanesorsen arm (n = 14 (42.4%)) than in the placebo arm (n = 1 (3.0%)) discontinued the 52-week treatment phase; in nine patients in the volanesorsen arm, adverse events were stated as the reason for discontinuation. The treatment and observation duration also differed between the treatment groups; in the median (min, max) the duration of treatment was 346 (57, 372) days in the volanesorsen arm and 358 (163, 379) days in the placebo arm. The total observation period was 360 (67, 465) days in the volanesorsen arm and 389 (163, 459) days in the placebo arm. However, no adjusted effect estimator (including appropriate statistical comparisons) or time-to-event analyses were presented for the evaluation of the data despite different treatment and observation periods. The risk of bias of the APPROACH study is therefore estimated to be high overall.

In the overall view, there is a hint for a non-quantifiable additional benefit in terms of the significance of the evidence.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Waylivra® with the active ingredient volanesorsen. Waylivra® was approved as an orphan drug and is indicated as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate.

For the benefit assessment, the pharmaceutical company presents the results of the pivotal, randomised, blinded, placebo-controlled APPROACH Phase III study, which is the basis for marketing authorisation as well as supplementary results of the randomised, blinded, placebo-controlled COMPASS Phase III study and the open-label, single-arm, long-term APPROACH OLE study.

The additional data from the COMPASS study are not considered for the benefit assessment because less than 10% of the patients had FCS according to the present therapeutic indication, and the treatment duration is significantly shorter than in the APPROACH study. Because of the high risk of bias and the questionable transferability to everyday clinical care, the supplementary data of the uncontrolled APPROACH OLE study will also not be considered.

No statements on the extent of the additional benefit can be derived from the data on mortality.

In the morbidity category, a statistically significant difference in favour of volanesorsen compared with placebo after a treatment duration of 3, 6, and 12 months was shown for the primary endpoint “change in the percentage of fasting triglyceride levels”. The parameter has a clinical relevance in the diagnosis and follow-up of the disease. In the present therapeutic indication, the triglyceride levels in the blood is a clinically relevant parameter, which is used

for diagnosis and therapy control. Beyond that, however, no valid data could be identified to show what effect a certain change in triglyceride levels in FCS patients has on patient-individual symptomatology or on the risk of acute pancreatitis. No statements on the extent of the additional benefit can be derived from the data on morbidity.

Nor can any statements on the extent of the additional benefit be derived from the data on quality of life and side effects.

The risk of bias of the APPROACH study is estimated to be high overall because no adjusted effect estimator (including appropriate statistical comparisons) or time-to-event analyses were presented for the evaluation of the data despite different treatment and observation periods.

In the overall view, for volanesorsen for the treatment of adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate, there is a hint for a non-quantifiable additional benefit for volanesorsen because the scientific data basis does not allow quantification.

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

The number of patients is the target population in the statutory health insurance (SHI). The G-BA bases the resolution on the estimate of the number of patients derived by the pharmaceutical company in the dossier. However, the number of patients indicated is subject to uncertainties. The number of patients in the SHI target population is calculated by the pharmaceutical company on the basis of literature data on the prevalence rate of patients with FCS. Because of the lack of robust data and because the pharmaceutical company does not further limit the target population to FCS patients at high risk for pancreatitis who have had an inadequate response to diet and triglyceride-lowering therapy, a high degree of uncertainty must be assumed in the data on the target population.

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 Waylivra® (active ingredient: volanesorsen) at the following publicly accessible link (last access: 19 September 2019):

https://www.ema.europa.eu/en/documents/product-information/waylivra-epar-product-information_de.pdf

Treatment with volanesorsen should only be initiated and monitored by physicians who are experienced in the treatment of patients with familial chylomicronemia syndrome (FCS).

This medicinal product was approved under “special conditions”. This means that further evidence of the benefit of the medicinal product is anticipated. The EMA will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

In accordance with the specifications of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide officially approved training material for medical personnel, including an information package for patients. In particular, the training material contains relevant information on

thrombocytopenia and heavy bleeding as well as recommendations on monitoring thrombocytes, including recommendations on dose adjustment before and during treatment.

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 February 2020).

The recommended initial dose of volanesorsen is 285 mg once a week for the first three months. After three months, the dosage should be reduced to 285 mg every two weeks. If the decrease in serum triglyceride is insufficient, the frequency can be increased to once a week and maintained after six months provided that it causes a significant additional decrease in triglyceride levels.

In general, initial induction schemes for cost representation are not taken into account because the present indication is a chronic disease with continuous need for therapy.

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 varies from patient to patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, time intervals between individual treatments, and for the maximum treatment duration if indicated in the product information.

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Volanesorsen	1 × every 7 days	52.1	1	52.1
	1 × every 14 days	26.1	1	26.1

Usage and consumption:

Designation of the therapy	Dosage	Dose/patient/ treatment days	Consumption by potency/treat ment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Volanesorsen	285 mg	285 mg	1 × 285 mg	52.1	52.1 × 285 mg
	285 mg	285 mg	1 × 285 mg	26.1	26.1 × 285 mg

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 130 a 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.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Volanesorsen	1 SFI	€ 20,281.43	€ 1.77	€ 1,155.00	€ 19,124.66
Abbreviations: SFI = solution for injection					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 February 2020

Costs for additionally required SHI services:

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

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

Designation of the therapy	Description of the service	Number	Costs per unit	Costs per patient per year
Medicinal product to be assessed				
Volanesorsen	Thrombocyte counting (GOP 32037)	27.1	€ 0.25	€ 6.78

3. Bureaucratic costs

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

4. Process sequence

On 28 June 2019, the pharmaceutical company submitted a dossier for the benefit assessment of volanesorsen to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 November 2019 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 6 December 2019.

The oral hearing was held on 18 December 2019.

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

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 11 February 2020, and the proposed resolution was approved.

At its session on 20 February 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	12 November 2019	Information of the benefit assessment of the G-BA
Working group Section 35a	17 December 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	18 December 2019	Conduct of the oral hearing
Working group Section 35a	14 January 2020 4 February 2020	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal Products	11 February 2020	Concluding discussion of the draft resolution
Plenum	20 February 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 20 February 2020

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

Prof. Hecken