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 Givosiran (Acute Hepatic Porphyria, ≥ 12 Years)

of 15 October 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 according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V. Proof of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy need not 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 (VerfO) of the G-BA 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 twelve 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 proof in accordance with Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medicinal 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 in comparison 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). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is deemed to have been 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, in the case of 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 of the G-BA must be completed within three months of the relevant date for submission of the proof 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 givosiran in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 April 2020. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, number 1 VerfO on 14 April 2020.

Givosiran for the treatment of acute hepatic porphyria (AHP) in adults and adolescents aged 12 years and older is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half 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 assess the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 15 July 2020 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), 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 assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G20-07) 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 assessed 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 - 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of givosiran.

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:

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.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of givosiran (Givlaari) in accordance with the product information

Givosiran is indicated for the treatment of acute hepatic porphyria (AHP) in adults and adolescents aged 12 years and older.

2.1.2 Extent of the additional benefit and significance of the evidence

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

Indication of a considerable additional benefit

Justification:

The Phase III ENVISION (ALN-AS1-003) pivotal study is used for the benefit assessment. According to the inclusion criteria, the study included patients ≥12 years with a documented diagnosis of acute hepatic porphyria (AHP), including acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), porphyria variegata (PV), or ALAD deficiency porphyria (ADP).

However, the study population consists only of adult patients aged 18 years and older. Of these, approx. 95% have acute intermittent porphyria. 5 of the 94 patients in the study have one of the rarer forms of AHP.

The study is divided into a 2-month screening phase, a 6-month randomised, double-blind, and placebo-controlled treatment phase, a non-controlled extension phase of up to 29 months, and a one-month follow-up phase (three months in the case of early discontinuation). 94 patients were randomised to the intervention and placebo arm at a ratio of 1:1. Prerequisite for inclusion was an active disease with at least 2 porphyria attacks, including hospitalisation, emergency treatment, or i.v. treatment with haemin at home within the last 6 months before screening. The study is being conducted in 18 countries (US, Canada, Mexico, Japan, South Korea, Taiwan, Bulgaria, Denmark, Germany, Finland, France, Great Britain, Italy, Netherlands, Poland, Sweden, Spain, Australia) and has not yet been completed (start of study was in December 2017).

<u>Mortality</u>

In the ENVISION study, deaths were recorded as an adverse event (AE). No deaths occurred during the study period.

<u>Morbidity</u>

Acute porphyria attacks

The occurrence of a porphyria attack is a patient-relevant event. During the study, potential porphyria attacks were recorded in an electronic diary by the patients themselves or their carers. The attacks were confirmed as acute porphyria attacks by the study centre if all the following criteria were met:

- Acute episode of neurovisceral pain in the abdomen, back, chest, extremities, and/or limbs

- No other medically determined cause
- Required treatment with dextrose (i.v.) or haemin (i.v.), carbohydrates or analgesics or other medications such as antiemetics in a dose or frequency that exceeds the usual daily patient-individual dose

Acute porphyria attacks were also divided into four non-overlapping components depending on the treatment of the attacks:

- Porphyria attacks requiring hospitalisation
- Porphyria attacks requiring emergency treatment
- Porphyria attacks requiring home administration of haemin (i.v.)
- Porphyria attacks not requiring home administration of haemin (i.v.)

A combined endpoint consisting of three attack components (porphyria attacks requiring hospitalisation, emergency treatment or home haemin administration (i.v.)) was defined as the primary analysis.

For the benefit assessment, all acute attacks of porphyria identified in the study are considered relevant. Accordingly, the number of all porphyria attacks during the treatment period is taken into account for the assessment of the additional benefit. In addition, evaluations of the annual attack rate and absence from attack are taken into account. The annual attack rate indicates how many attacks a patient has suffered on average over one year of treatment with givosiran or placebo. The absence of attacks indicates the number of patients who did not have an attack during the treatment period.

In addition, the evaluations regarding the number of attacks for the individual components “porphyria attacks requiring hospitalisation”, “porphyria attacks requiring emergency treatment”, and “porphyria attacks requiring home haemin administration (i.v.)” are also considered for the benefit assessment. Because the individual components are presented, the additional presentation of the composite primary endpoint is omitted.

With regard to inpatient or emergency outpatient care, regional differences in availability and utilisation can occur. It is unclear whether these have been fully compensated by randomisation without stratification by country or centre. These regional differences also lead to uncertainties in the transferability of the results to the German health care context.

During the 6-month treatment period, 317 acute porphyria attacks occurred in 40 patients in the placebo arm and 109 acute porphyria attacks in 30 patients in the givosiran arm. The number of attacks or the calculated annual attack rate differs significantly between the treatment arms in favour of givosiran. The number of patients without an attack (absence of attacks) also differs significantly between treatment arms in favour of givosiran.

In detail, there was a statistically significant difference in the number of attacks between the treatment arms in favour of givosiran in the porphyria attacks requiring emergency treatment. The number of porphyria attacks requiring hospitalisation or home haemin administration (i.v.) does not differ significantly between the treatment arms.

Pain intensity using Item 3 of the BPI-SF (Brief Pain Inventory - Short Form)

The BPI-SF is a patient-reported pain questionnaire. The questionnaire consists of 15 items; however, only Item 3 was used in the study. Item 3 enquires about the worst pain intensity of the last 24 hours. Pain is rated on a scale of 0 to 10 with 0 points for no pain and 10 points for the worst pain imaginable. The endpoint was recorded daily via the electronic patient diary.
During the screening phase the baseline value was formed as the mean of entries of a minimum of 4 and a maximum of 7 attack-free days. During the treatment phase, an average weekly value was determined.
The endpoint was evaluated as group difference in the "Area Under the Curve" (AUC) and the mean change between baseline and each study week.
Only the values for the mean change are shown in the resolution because both evaluations are based on the mean weekly value calculated. In the present case, it is therefore not assumed that the evaluation via the AUC ensures better detection of high levels in acute attacks.

An uncertainty results from the use of only one item from a complex questionnaire. The relevance, applicability, and reliability of Item 3 of the BPI-SF was demonstrated for patients with AHP; information on change sensitivity and clinical relevance of a change could not be identified. The pain intensity at baseline was calculated for each patient exclusively from days without attacks, whereas during the course of the study, pain was determined based on days without and with attacks. This procedure can lead to a bias of the pain intensity at baseline.

The endpoint is considered in the benefit assessment despite the remaining uncertainties.

In the differences of the mean changes, there was no statistically significant difference between the two treatment arms.
The AUC changes on average (SEM) by −12.06 (4.34) in the givosiran arm and by −0.27 (4.46) in the placebo arm. The difference is not statistically significant (mean difference [95% CI]: −11.80 [−24.15; 0.56]; p = 0.0610.

Fatigue using Item 3 of the BFI (Brief Fatigue Inventory)

The BFI is a patient-reported questionnaire to record the severity of the fatigue and the extent of the resulting impairment in daily life. The questionnaire contains 10 items. Item 3 used in the study records the strongest extent within the last 24 hours. It is rated on a scale of 0 to 10 with 0 points for "no fatigue" and 10 points for "worst fatigue imaginable".
The endpoint was recorded daily via the electronic patient diary.
The determination of the baseline values, the mean weekly values during the treatment phase, and the evaluation as group difference in AUC and mean changes was carried out in the same way as for Item 3 of the BPI-SF.

An uncertainty results from the use of only one item from a complex questionnaire. The relevance and applicability of Item 3 of the BFI was demonstrated for patients with AHP; information on change sensitivity, and clinical relevance of a change could not be identified. The baseline value of each patient was also formed for fatigue exclusively from days without attacks, whereas during the course of the study, fatigue was determined based on days without and with attacks. This procedure can lead to a bias of the fatigue at baseline.

The endpoint is considered in the benefit assessment despite the remaining uncertainties.

In the differences of the mean changes, there was no statistically significant difference between the two treatment arms.
The AUC changes on average (SEM) by −10.46 (4.35) in the givosiran arm and by −3.68 (4.46) in the placebo arm. The difference is not statistically significant (mean difference [95% CI]: 6.79 [−19.09; 5.51]; p = 0.2759).

Nausea using NRS (Numeric Rating Scale)

Nausea was recorded via an 11-point NRS, which asked for the worst nausea of the last 24 hours. 0 points stands for “no nausea” and 10 points for “worst nausea imaginable”.
The endpoint was recorded daily via the electronic patient diary.
The determination of the baseline values, the mean weekly values during the treatment phase, and the evaluation as group difference in AUC and mean changes was carried out in the same way as for Item 3 of the BPI-SF.

The relevance and applicability in patients with AHP was demonstrated for the nausea endpoint using NRS; information on reliability, change sensitivity, and clinical relevance of a change could not be identified. The endpoint appears adequate for the assessment of nausea despite the limitations. It is thus considered in the benefit assessment.

In the differences of the mean changes, there was no statistically significant difference between the two treatment arms.
The AUC changes on average (SEM) by 1.60 (3.27) in the givosiran arm and by −3.00 (3.36) in the placebo arm. The difference is not statistically significant (mean difference [95% CI]: 4.59 [−4.66; 13.84]; p = 0.3266).

General health status using the EQ-5D-VAS (European Quality of Life 5 Dimensions 5 Level, Visual Analogue Scale)

The questionnaire includes five dimensions (mobility, self-care, ordinary activities, pain/comfort, anxiety/depression), a visual analogue scale (VAS), and an overall benefit value. The EQ-5D-VAS measures the self-assessment of health on a 20 cm scale. The extremes are “best conceivable health status” (100 on the scale) and “worst conceivable health status” (0 on the scale). The EQ-5D-VAS is a valid and reliable instrument for surveying the general health status. The evaluation was carried out as group difference in the mean changes of the treatment groups.

At month 6, there was no statistically significant difference between the treatment arms.

General health status using PGI-C

The PGI-C (Patient Global Impression of Change) is a question that uses a 7-point scale (from “much much better” to “much much worse”) to answer the perceived change in general health status since the start of study. The evaluation was descriptively intended as the number and proportion of patients in the categories “improved” and “not changed or deteriorated” (all others). No data were available for 8 patients from the control arm and 11 patients from the givosiran arm. For the benefit assessment, the conservative evaluation in which patients with missing values were counted in the category “not changed or deteriorated” (all others) was used. A group comparison was planned for the respective shares in the “improved” category.

For the improvement category, there is a significant difference in favour of givosiran compared with placebo.

With the written statement, the pharmaceutical company submitted a post-hoc evaluation for patients with deteriorations in the PGI-C. Patients with missing values were evaluated together with patients without deterioration as one category; this leads to a potentially biased result.

As a result, there is no statistically significant difference between the treatment arms for the deterioration category.

Quality of life

SF-12

The SF-12 (Short Form 12) serves as a generic questionnaire for recording symptomatology, functioning, and quality of life. It is a short form of the SF-36 questionnaire and thus contains only 12 of the 36 items. It nevertheless covers (with one or two individual items each) the complete field of the 8 sub-scales and the two domains “Physical Health” and “Mental Health”. The “Physical Component Summary (PCS)” and “Mental Component Summary (MCS)” can reach values between 0 and 100, whereby a value of 0 indicates the worst health status and a value of 100 indicates the best health status.
In the resolution, the group differences in the mean change (mean differences) are presented.

SF-12 is considered to be sufficiently reliable and valid; information on change sensitivity and thresholds for clinically relevant differences could not be identified.

In the course of the written statement procedure, responder analyses of the PCS and MCS with the Minimal Important Differences (MID) of 2, 3, and 5 were submitted. Because the validity of the respective MIDs is unclear, the responder analyses are not considered for the benefit assessment.

The changes from baseline to month 6 in the PCS were statistically significantly stronger in the givosiran arm than in the placebo arm. In the absence of a validated irrelevance threshold to assess the group difference, the 95% CI of the standardised mean difference (Hedges’ g) was calculated. Because Hedges’ g. (0.46 [0.05; 0.88]) is not completely outside the irrelevance range of −0.2 to 0.2, it cannot be derived with sufficient certainty that this is a clinically relevant effect. The result not taken into account for the assessment of the additional benefit.

At month 6, there was no statistically significant difference between the treatment arms in the MCC of the SF-12.

Side effects

Adverse events (UA) were recorded from the time of administration of the first dose of the study medication for the entire duration of the study and serious AE (SAE) from the time of signing the informed consent form. Porphyria attacks were recorded separately as efficacy endpoints.

Adverse events occurred in most patients in both study arms. Among other things, changes in laboratory parameters were recorded as AE; the patient relevance of laboratory parameters remains unclear.

The number of patients with severe AE and the number of patients with SAE do not differ significantly between treatment arms; no effect estimator could be calculated for the number of patients with therapy discontinuation or with discontinuation of study medication because of an AE.

Larger differences (≥ 10% in one arm) between the groups occurred in the system organ class "General disorders and administration site conditions", including the preferred terms "fever" and "reaction at the injection site" as well as in the system organ class "Renal and urinary disorders" with the preferred term "chronic kidney disease" and in the preferred term "nausea"(system organ class "gastrointestinal disorders"). With the exception of the preferred term "fever", more events occurred in each of the givosiran arms. With the exception of the preferred term "nausea", for which there was a statistically significant difference to the detriment of givosiran, there was no statistically significant difference between the treatment arms, or no effect estimator could be calculated.

Overall assessment

For the treatment of acute hepatic porphyria (AHP) in adults and adolescents aged 12 years and older, results on mortality, morbidity, quality of life and side effects from a 6-month randomised, blinded and placebo-controlled study phase based on the pivotal ENVISION (ALN-AS1-003) Phase III study are available.

No deaths occurred in the ENVISION study.

In the morbidity category, there was a statistically significant advantage of givosiran compared with placebo for the clinically relevant endpoint "acute porphyria attacks" for both the number of attacks or the calculated annual attack rate and for the number of patients without attacks (absence of attacks). In detail, there was a statistically significant advantage of givosiran compared with placebo for porphyria attacks requiring emergency treatment. The results on health status, assessed by patients using Patient Global Impression of Change, support the result in the endpoint porphyria attacks: In the givosiran arm, the frequency with which caregivers recorded an improvement in health was significantly higher.

For the other morbidity endpoints relevant for assessment, pain intensity, fatigue, nausea, and health status using EQ-5D-VAS, there are no statistically significant differences between the treatment arms.

In the quality of life category, there is a statistically significant advantage of givosiran compared with placebo in the Physical Component Summary (PCS) of the SF-12. However this cannot be taken into account for the assessment of additional benefit because of uncertain clinical relevance. In the Mental Component Summary (MCS) of the SF-12, there is no statistically significant difference between the treatment arms.

In the endpoint category side effects, the overall rates show no relevant differences between the treatment groups.

In summary, the statistically significant and clinically relevant advantages of givosiran compared with placebo in the morbidity category are considered to be significant overall on

the basis of the criteria in Section 5, paragraph 7 of the AM-NutzenV, taking into account the severity of the condition, the written statements, and the oral hearing.

Significance of the evidence

The ENVISION study (ALN-AS1-003) is a randomised, double-blind, placebo-controlled Phase III study with a treatment period of 6 months. The purpose of the study was to assess the additional benefit in the indication acute hepatic porphyria.

Despite some uncertainties, the risk of bias at the study level is estimated as low across all endpoints.

At the endpoint level, the overall certainty of results is limited because of the small study size and, for the endpoints pain intensity, fatigue, and nausea because of the determination of baseline values.

There are further uncertainties regarding the significance of the study results because no patients between 12 and 18 years of age and only very few patients with rare forms of AHP were included in the study.

In the overall view, there is an indication of an additional benefit in terms of the significance of the evidence.

2.1.3 Summary of the assessment

The present assessment refers to the benefit assessment of the new medicinal product “Givlaari” with the active ingredient “givosiran”. Givosiran is approved as an orphan drug for the treatment of acute hepatic porphyria (AHP) in adults and adolescents aged 12 years and older. For the benefit assessment, the pharmaceutical company presents the Phase III ENVISION (ALN-AS1-003) pivotal study in which givosiran was compared with placebo in a 6-month, randomised, double-blind, controlled treatment phase. Only adult patients aged 18 and over were included in the study. Of these, approx. 95% have acute intermittent porphyria (AIP). 5 of the 94 patients in the study have one of the rarer forms of AHP.

Based on the ENVISION study, results on mortality, morbidity, quality of life, and side effects are available.

No deaths occurred. In the morbidity category, there was a statistically significant advantage of givosiran compared with placebo for the clinically relevant endpoint “acute porphyria attacks” for both the number of attacks or the calculated annual attack rate and for the number of patients without attacks (absence of attacks). The results on health status, assessed by patients using Patient Global Impression of Change, also show a statistically significant advantage of givosiran compared with placebo.
For the other morbidity endpoints relevant for assessment, pain intensity, fatigue, nausea, and health status using EQ-5D-VAS, there are no statistically significant differences between the treatment arms.
In the quality of life category, there is a statistically significant advantage of givosiran compared with placebo in the Physical Component Summary (PCS) of the SF-12. However this cannot be taken into account for the assessment of additional benefit because of uncertain clinical relevance. In the Mental Component Summary (MCS) of the SF-12, there is no statistically significant difference between the treatment arms.

In the endpoint category side effects, the overall rates show no relevant differences between the treatment groups.

Despite some uncertainties, the risk of bias at the study level is estimated as low across all endpoints. The certainty of results is limited overall because of the small size of the study, the lack of data from patients between 12 and 18 years of age, or a very small proportion of data from patients with rare forms of AHP as well as for the endpoints pain intensity, fatigue, and nausea because of the determination of baseline values.

In the overall view, there is an indication of a considerable additional benefit of givosiran compared with placebo.

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). These are based on the data from the pharmaceutical company's dossier. The figures are based on data from a routine data analysis, which contained the number of patients in Germany for whom the ICD-10-GM diagnostic code E80.2 (other porphyria) was documented between 2013 and 2018. The number of patients in the target population of the SHI system was determined based on further restrictions with regard to diagnosis and age or based on the restriction to patients undergoing hospitalisation or emergency treatment or prescription or application of haemin from 2013 to the end of 2018.

This information is subject to uncertainties. Because of the exclusion of patients for whom the diagnosis code E80.2 was not documented in 2018 and the exclusion of patients without AHP-associated hospitalisation or emergency treatment or the use of haemin, the number of patients determined in the SHI target population is likely to be underestimated.

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 Givlaari® (active ingredient: givosiran) at the following publicly accessible link (last access: 29 July 2020):
https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_de.pdf

Treatment with givosiran should only be initiated and monitored by physicians who are experienced in the treatment of patients with acute hepatic porphyria.

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: 15 September 2020).

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

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

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Givosiran	1 × monthly	12	1	12

Usage and consumption:

According to the product information, the recommended dose of givosiran is 2.5 mg/kg once a month, administered by subcutaneous injection. The dosage is based on the actual body weight. For the calculation of the dosages as a function of body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis[2.]. The lower limit was the average body weight of a 12-year-old adolescent (47.1 kg); the upper limit was the average body weight of an adult (77.0 kg).

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					
Givosiran	2.5 mg/kg	12-year-old adolescent: 117.75 mg	1 × 189 mg –	12	12 × 189 mg –
		Adults: 192.5 mg	2 × 189 mg		24 × 189 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.

2 German Federal Office For Statistics, Wiesbaden 2018: http://www.gbe-bund.de/

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					
Givosiran	1 SFI	€ 55,002.82	€ 1.77	€ 3,221.88	€ 51,779.17
Abbreviations: SFI = solution for injection					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 September 2020

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be assessed 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.

No additionally required SHI services are taken into account for the cost representation.

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 14 April 2020, the pharmaceutical company submitted a dossier for the benefit assessment of givosiran to the G-BA in due time in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 July 2020 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 5 August 2020.

The oral hearing was held on 24 August 2020.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI

umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 6 October 2020, and the proposed resolution was approved.

At its session on 15 October 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	12 November 2019	Information of the benefit assessment of the G-BA
Working group Section 35a	19 August 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	24 August 2020	Conduct of the oral hearing
Working group Section 35a	2 September 2020 16 September 2020 30 September 2020	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee on Medicinal Products	6 October 2020	Concluding discussion of the draft resolution
Plenum	15 October 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 15 October 2020

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

Prof. Hecken