Gemeinsamer Bundesausschuss

Justification

of 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 Angiotensin II Acetate (hypotension)

of 6 January 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 of the medical product 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the active ingredient angiotensin II acetate in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 July 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 15 July 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 15 October 2021, 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 angiotensin II acetate compared with the appropriate comparator therapy could be determined on the basis of the

dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods was not used in the benefit assessment of angiotensin II acetate.

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 Angiotensin II Acetate (Giapreza) according to the product information

"GIAPREZA is indicated for the treatment of refractory hypotension in adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines and other available vasopressor therapies."[1]

Therapeutic indication of the resolution (resolution of 06.01.2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of Catecholamines and other available vasopressor therapies

An optimised standard therapy.

Indication: Standard therapy includes, in particular, fluid substitution, vasopressors and antibiotics.

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] The Federal Institute for Drugs and Medical Devices (BfArM) has confirmed that the German marketing authorisation text is a translation error, so that the benefit assessment is based on the "conjunction and" (analogous to the English marketing authorisation text).

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, in principle, 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 Federal Joint Committee has already determined the patient-relevant advantage 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. Except angiotensin II acetate, no other medicinal product is currently approved for the treatment of refractory hypotension in adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines and other available vasopressor therapies.

In the therapeutic indication for the treatment of anaphylactic, septic and neurogenic shock, the following medicinal products are considered in addition to colloid or crystalloid solution, taking into account the suitability of the medicinal product for the patient:

norepinephrine, dopamine, epinephrine, argipressin, dexamethasone dihydrogen phosphate disodium, dimetindene maleate, triamcinolone acetonide.

on 2. In the present therapeutic indication, a non-medicinal treatment is not considered.

on 3. In the mentioned therapeutic indication, there are no resolutions of the G-BA.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic 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 the robust evidence on treatment options in the present therapeutic indication is limited overall. Currently, no medicinal product is approved for the targeted treatment of refractory hypotension in adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines and other available vasopressor therapies.

Based on the currently available evidence, the treatment of patients with distributive shock in the mentioned therapeutic indication is carried out as part of a standard therapy, which includes, in particular, fluid substitution and vasopressors. This applies both to patients who remain hypotensive on therapy with catecholamines and to those who remain hypotensive on therapy with catecholamines and other available vasopressor therapies.

Since the therapeutic indication focuses on the treatment of hypotension in adults with septic or other distributive shock, the treatment of an underlying disease is also indicated as part of the best possible care of the patient. Thus, antibiotics should be used to treat the infection that caused the septic shock.

Accordingly, an optimised standard therapy for the treatment of anaphylactic, septic and neurogenic shock is defined as the appropriate comparator therapy.

It is assumed that the patients in both study arms will receive optimum intensive care treatment, if medically necessary. Standard therapy includes, in particular, fluid substitution, vasopressors and antibiotics. If there is no further possibility of optimisation, it must be documented and explained that any other existing treatment options are not suitable or have been exhausted. If optimised standard therapy is offered in the comparator arm, placebo (in the comparator arm) may also be given for the purpose of blinding.

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 angiotensin II acetate is assessed as follows:

Adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of Catecholamines and other available vasopressor therapies

An additional benefit is not proven.

Justification:

For the benefit assessment, the pharmaceutical company presents the multicentre, randomised, double-blind ATHOS-3 study, in which angiotensin II acetate is investigated versus placebo in addition to vasopressor therapy in each case. 344 adults with a catecholamine-refractory hypotension, defined as a total catecholamine requirement of > 0.2 µg/kg/min over 6-48 hours to maintain mean arterial pressure (MAP) at a level of 55-70 mm Hg, and clinical high-output shock were enrolled in the study. Patients should have received adequate volume replacement and have a cardiovascular SOFA[2] score of 4. Prior to randomisation, patients in the study received 6 to 48 hours of vasopressor therapy, optimised to achieve a target MAP of ≥ 65 mm Hg, if possible. Patients who met the inclusion criteria after this period were then randomised to the angiotensin II acetate or placebo treatment arms (1:1). Stratification was by MAP[3] at screening visit (< 65 / ≥ 65 mm Hg) and APACHE II score[4] (≤ 30 / 31-40 / ≥ 41 points). Of those randomised, 163 subjects in the angiotensin II arm and 158 in the placebo arm were treated with the study medication (mITT population[5]). On average, the patients were about 63 years old, with the majority of patients being male (56% in the angiotensin arm, 65% in the placebo arm). About three quarters of the subjects came from North America, about 16% from Australia/New Zealand and about 11% from Europe. The mean MAP at the start of treatment was about 66 mm Hg.

Depending on the treatment phase and MAP, study medication and vasopressor therapy were adjusted over 48 hours in both study arms, with no changes to the vasopressor dose for the period from 0 to 3 hours, if possible. In the angiotensin II arm, a maximum dose of 200

[2] SOFA = Sequential Organ Failure Assessment

[3] MAP = Mean Arterial Pressure

[4] APACHE = Acute Physiology and Chronic Health Evaluation.

[5] mITT = modified intention to treat

ng/kg/min was allowed in the period from 0 to 3 hours, but the approved maximum dose of angiotensin II acetate in this period is 80 ng/kg/min according to the product information. About 16% of the patients received a dose above the approved maximum dose during this period.

The average treatment duration was 47 hours in the angiotensin II arm and 40 hours in the placebo arm. All patients should be observed for at least 7 days (or at least 3 days after discontinuation of the study medication) and examined in an additional follow-up 28 days after the start of treatment.

The primary endpoint of the study was MAP response rate after 3 hours. Patient-relevant secondary endpoints were overall mortality and endpoints for morbidity and adverse events (AEs).

Relevant population for the benefit assessment

At the time of the dossier submission and benefit assessment, there was a translation error in the German product information. The German text of the product information "GIAPREZA is indicated for the treatment of refractory hypotension in adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and the application of catecholamines **or** other available vasopressor therapies (see section 5.1)." differs from the original wording in the English marketing authorisation text: *"GIAPREZA is indicated for the treatment of refractory hypotension in adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines **and** other available vasopressor therapies (see section 5.1)".*

Upon enquiry with the German regulatory authority, the Federal Institute for Drugs and Medical Devices (BfArM), this translation error was confirmed, so that the benefit assessment is based on the "conjunction and" (analogous to the English marketing authorisation text). At the time of the adoption of the resolution, no amended German product information was available; according to information from the BfArM, an amendment will be made in the near future.

In addition, the BfArM was asked about the approved indication due to the discussion from the oral hearing. In reply, the BfArM confirmed that the indication includes both the treatment situation "in addition to catecholamines" ("second-line") and patients who remain hypotensive ("third-line") under therapy with catecholamines and other available vasopressor therapies.

The interpretation of the wording of the indication by the BfArM is based on the explanations in the product information and the EPAR[6].

Against this background, the total population of the ATHOS-3 study is relevant for the benefit assessment. This total population includes patients who received one or more catecholamines as previous therapy and possibly an additional vasopressor. A large proportion (about 70%) of the patients in the study had been given at least two vasopressors as previous therapy.

The pharmaceutical company submits both the results of the total population and of a sub-population of the ATHOS-3 study, which only includes those patients who were previously treated with at least two vasopressors, as this sub-population corresponds to the population

[6] see explanations in the EPAR https://www.ema.europa.eu/en/documents/assessment-report/giapreza-epar-public-assessment-report_en.pdf on page 82: "Therefore, the indication can be interpreted as a second-line therapy, in addition to catecholamines, or third-line therapy in addition to catecholamines and other available vasopressor therapies, which is consistent with the data generated by the company, [...]"

relevant to the marketing authorisation in the company's view. The pharmaceutical company exclusively uses the results of the sub-population to determine the additional benefit. This sub-population was evaluated by IQWiG in an addendum following the oral hearing.

Due to the clarification of the BfArM, it can be assumed that the submitted sub-population does not correspond to the overall approved therapeutic indication of angiotensin II acetate and thus, the data of the sub-population are not sufficient for the assessment of the additional benefit of angiotensin II acetate. Consequently, the total population is used here.

About the implementation of the appropriate comparator therapy

An optimised standard therapy was defined as the appropriate comparator therapy, which includes, in particular, fluid therapy, therapy with vasopressors and therapy with antibiotics. Overall, the therapy used in the ATHOS-3 study can be considered a sufficiently optimised standard therapy.

With regard to fluid therapy, inclusion in the ATHOS-3 study was subject to the prerequisite that all patients had received fluid therapy with at least 25 ml/kg of a crystalloid or colloid solution prior to the start of vasopressor therapy and that adequate volume replacement was available according to the principal investigator. After the initial fluid therapy, further fluid administration should be avoided, if possible, but the administration of up to 750 ml of fluid was allowed during the first 3 hours of treatment. The use of colloids and crystalloids in the ATHOS-3 study is also appropriate, as the guidelines[7,8] only recommend the use of crystalloids, but this recommendation is only based on the fact that colloids are associated with higher costs. Even though the study used an initial fluid therapy of at least 25 ml/kg instead of the minimum 30 ml/kg recommended in the guidelines, the central venous pressure (CVP) in the patients was about 13 mm Hg at the start of study, slightly above the target of 8-12 mm Hg[9], recommended for “early goal-directed therapy”. Overall, the fluid therapy used in the ATHOS-3 study is therefore assessed as appropriate.

After fluid therapy, the study patients received vasopressor therapy, which was adjusted 6 to 48 hours before starting treatment with the study medication to achieve a target MAP of ≥ 65 mm Hg, if possible. Almost all patients received norepinephrine, about 51% also received another vasopressor and about 20% received more than two vasopressors. At the start of treatment, MAP averaged 66 mm Hg. No changes in vasopressor dose were to be made for 3 hours from the start of treatment with study medication, but adjustment was possible if the patient remained hypotensive (MAP ≤ 59 mm Hg) or became hypertensive (MAP ≥ 85 mm Hg) despite adjustment of study medication. In addition, a dose increase of the vasopressor therapy was possible at any time at the discretion of the principal investigator.

Mean MAP levels increased in both the angiotensin and placebo arms during the first 3 hours of treatment. In addition, the pharmaceutical company states that adjustments in vasopressor therapy were made in 47 patients in the placebo arm during the first 3 hours. Overall, it is therefore considered that the ATHOS-3 study assumes sufficiently optimised vasopressor therapy despite the limitations in the first 3 hours.

[7] S3 Guideline Sepsis – Prevention, Diagnosis, Therapy and Follow-up, 2018 https://www.awmf.org/uploads/tx_szleitlinien/079-001l_S3_Sepsis-Praevention-Diagnose-Therapie-Nachsorge_2020-03_01.pdf

[8] Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock, 2016, https://dx.doi.org/10.1007/s00134-017-4683-6

[9] Rivers et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345(19): 1368-1377. https://dx.doi.org/10.1056/NEJMoa010307.

Furthermore, in the ATHOS-3 study, about 99% of the patients were treated with systemic anti-infectives. Information such as type and dosage of therapy is not available, but the pharmaceutical company states that it is certain that all patients with suspected or confirmed sepsis received antibiotics and that in the present life-threatening situation, it can be assumed that all antibiotic therapy options were exhausted and, in accordance with general practice, therapy was adjusted if a pathogen was detected. Since approx. 80% of the patients had confirmed sepsis, it is assumed that an appropriate therapy with antibiotics was carried out in the study to treat the underlying disease.

Overall, the therapy used in the ATHOS-3 study can be considered as a sufficiently optimised standard therapy despite the limitations in the study protocol, and it can be assumed that the patients received adequate care.

Irrespective of this, there are uncertainties regarding the transferability of the ATHOS-3 study to the German health care context. In the ATHOS-3 study, only about 10% of the study participants were from Europe. These European patients differed significantly from the rest of the patients in terms of their prognosis and the therapy used. In addition to these aspects, it is also unclear to what extent the therapy of European patients reflects the German care context, since different therapies are also approved within Europe and the standards of intensive care treatment may differ.

Results of the total population of the ATHOS-3 study[10]

Extent and probability of the additional benefit

Mortality

For overall mortality on day 28, there are no statistically significant differences between the treatment groups in the total population.

Morbidity

With regard to morbidity, there are no statistically significant differences between the treatment groups in the total population for the endpoint "discharge from the intensive care unit".

No usable data are available from the ATHOS-3 study for the endpoints "discontinuation of artificial respiration" and "discontinuation of renal replacement therapy".

Discontinuation of artificial respiration

The endpoint "discontinuation of artificial respiration" is defined as the period between the start of treatment and the end of artificial respiration. Evaluations with an observation period of 7 days are available in the dossier. These results show that a large proportion of patients were still receiving artificial respiration after 7 days, so that the median was not reached in this evaluation. The observation period of 7 days is therefore too short to obtain results of any significance.

[10] The total population of the ATHOS-3 study includes patients who received one or more catecholamines and possibly an additional vasopressor as previous therapy and are still hypotensive.

Discontinuation of renal replacement therapy

The endpoint "discontinuation of renal replacement therapy" is defined as the period between the start of treatment and discontinuation of renal replacement therapy and was evaluated post hoc as a regulatory requirement. The evaluations presented only take into account patients who had suffered acute kidney failure at the start of treatment, which necessitated renal replacement therapy. However, in the present therapeutic indication, all patients are basically at risk of developing acute kidney failure during the study period due to the potential deterioration of organ functions. The overall percentage of patients included in the evaluation is so small that a consideration of the patients with renal replacement therapy at the start of study alone does not allow any statements to be made for all patients in the study.

The results presented by the pharmaceutical company show that a large proportion of patients still required renal replacement therapy after 7 days, so that the median was not reached in this evaluation. The observation period of 7 days is therefore too short to obtain results of any significance.

MAP (Mean Arterial Pressure)

The endpoint "MAP response rate" was the primary endpoint in the ATHOS-3 study and is only presented additionally. MAP is a clinical parameter used in the treatment of shock to monitor circulatory stabilisation. Achieving and maintaining MAP is central to therapy management in this patient group. However, target values can vary from person to person. Furthermore, in the present acute disease situation, a direct assessment of an improvement in the health status and symptomatology is feasible. Therefore, the endpoint cannot be used to assess the additional benefit.

Quality of life

Quality of life was not recorded in the ATHOS-3 study.

Side effects

In the present therapeutic indication, the AEs that occurred are strongly overlaid by events of the underlying disease, as it manifests itself in a variety of symptoms due to the failure of various organs and the differentiation between side effects of the intervention and events of the underlying disease is thus not clearly possible. Therefore, results on side effects that include AEs that are due to the symptomatology of the underlying disease are interpreted as a mixture of symptomatology and adverse events.

For the side effects, there were no statistically significant differences between the treatment groups in the total population with regard to the endpoints "serious adverse events (SAE)", "discontinuation due to adverse events (AE)" and in detail for the specific AEs "embolism and thrombosis events (SAE)" and "peripheral ischaemia (SAE)".

No usable data are available for the endpoint “arrhythmias”. The results of the predefined evaluations (SMQ[11] cardiac arrhythmias and SMQ Torsades de Pointes/QT prolongation) are not submitted by the pharmaceutical company. Instead, an evaluation was presented on so-

[11] SMQ = Standardised MedDRA Query

called cardiac AEs of special interest, which, however, also included acute myocardial infarctions that do not count as arrhythmias according to the predefined evaluation via the SMQs.

Overall assessment

Results from the ATHOS-3 study are available for the assessment of the additional benefit of angiotensin II acetate compared to optimised standard therapy. The total population of the study is considered, since, according to information from the BfArM, the therapeutic indication includes both the treatment of patients in addition to catecholamines and those who remain hypotensive under therapy with catecholamines and other available vasopressor therapies. The data from the sub-population of patients who were previously treated with at least two vasopressors do not adequately represent the therapeutic indication for the assessment of the additional benefit of angiotensin II acetate.

However, there was no statistically significant difference between the treatment groups for mortality.

In the morbidity category, no statistically significant difference could be shown for the endpoint "discharge from the intensive care unit". No usable data are available for the endpoints "discontinuation of artificial respiration" and "discontinuation of renal replacement therapy".

No data were collected in the quality of life category.

In the side effects category, there were no statistically significant differences between the treatment arms.

In the overall assessment, there are neither advantages nor disadvantages for angiotensin II acetate compared to optimised standard therapy. It is found that an additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Giapreza" with the active ingredient "angiotensin II acetate".

Angiotensin II acetate is approved for the "treatment of refractory hypotension in adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines and other available vasopressor therapies."

The total population of the study is considered, since, according to information from the BfArM, the therapeutic indication includes both the treatment of patients in addition to catecholamines and those who remain hypotensive under therapy with catecholamines and other available vasopressor therapies.

The G-BA determined the optimised standard therapy (in particular, fluid substitution, vasopressors and antibiotics) as the appropriate comparator therapy.

The benefit assessment is carried out using the multicentre, randomised, double-blind ATHOS-3 study, in which angiotensin II acetate is tested against placebo in addition to vasopressor therapy in each case.

However, there was no statistically significant difference between the treatment groups for mortality.

In the morbidity category, no statistically significant difference could be shown for the endpoint "discharge from the intensive care unit". No usable data are available for the endpoints "discontinuation of artificial respiration" and "discontinuation of renal replacement therapy".

No data were collected in the quality of life category.

In the side effects category, there were no statistically significant differences between the treatment arms.

In the overall assessment, there are neither advantages nor disadvantages for angiotensin II acetate compared to optimised standard therapy.

It is found that an additional benefit is 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.

The stated range of approx. 3,980 to 37,625 patients is subject to uncertainties.

The lower limit results from the statements of the pharmaceutical company in the dossier. For the derivation of the patient numbers, the pharmaceutical company only takes into account those patients with distributive shock who have an intensive care stay with monitoring and selects them with the operation and procedure code (OPC) 8-932 (monitoring of respiration, heart and circulation with measurement of pulmonary arterial pressure). Overall, it is not comprehensible why this limitation of the target population was made, as the product information does not provide for this. Against this background, this figure is considered to be an underestimate of the number of patients in the target population. Without this limitation by means of OPS code 8-932, there is an upper limit of 37,625 patients in the SHI target population, which is considered to be possibly overestimated.

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 Giapreza (active ingredient: angiotensin II acetate) at the following publicly accessible link (last access: 01 December 2021):
https://www.ema.europa.eu/en/documents/product-information/giapreza-epar-product-information_en.pdf

Treatment with angiotensin II acetate should only be initiated and monitored by a specialist who is experienced in the treatment of shock. It is indicated as acute, in-patient 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 December 2021).

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.

Since the optimised standard therapy of refractory hypotension with septic or other distributive shock is patient-individual, no specific costs for the appropriate comparator therapy can be mentioned here. In addition, optimised standard therapy for the treatment of refractory hypotension with septic or other distributive shock and the underlying disease is provided in the context of both the medicinal product angiotensin II acetate to be assessed and the appropriate comparator therapy. Standard therapy includes, in particular, fluid substitution, vasopressors and antibiotics.

Generally, initial induction schemes are disregarded for cost representation. The maintenance dose is used to calculate the annual treatment costs. The maintenance dose of angiotensin II acetate should not exceed 40 ng/kg per minute according to the product information. Low doses of up to 1.25 ng/kg per minute can be used.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Angiotensin II Acetate	1 x 48 hours	1	2	2
+ Optimised standard therapy	different from patient to patient			
Appropriate comparator therapy				
Optimised standard therapy	different from patient to patient			

Consumption:

The time unit "days" is used to calculate the "number of treatments/ patient/ years", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For dosages depending on body weight or body surface area (BSA), the average body measurements were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[12].

[12] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

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					
Angiotensin II Acetate	1.25 ng/kg – 40 ng/bw kg/min	0.2772 mg - 8.8704 mg	1 x 2.5 mg - 2 x 2.5 mg	2	2 x 2.5 mg - 4 x 2.5 mg
+ Optimised standard therapy	different from patient to patient				
Appropriate comparator therapy					
Optimised standard therapy	different from patient to patient				

Costs:

Angiotensin II acetate is listed in the LAUER-TAXE® as a clinic pack. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 130 or Section 130a SGB V apply. The calculation is based on the purchase price of the clinic pack plus 19% value added tax, in deviation from the LAUER-TAXE® data usually taken into account.

The costs for the optimised standard therapy are different from patient to patient.

Costs of the medicinal products:

Medicinal product to be assessed		
Designation of the therapy	Packaging size	Cost of the single pack (plus value added tax)
Angiotensin II Acetate	10 CIS[13]	€ 1,500.00
+ Optimised standard therapy	different from patient to patient	

[13] A consumption of 2 - 4 packs is assumed from the container of 10 CIS.

Appropriate comparator therapy					
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
Optimised standard therapy	different from patient to patient				
Abbreviations: CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 December 2021

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be 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 26 February 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 15 July 2021, the pharmaceutical company submitted a dossier for the benefit assessment of angiotensin II acetate to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 1 VerfO.

By letter dated 15 July 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 angiotensin II acetate.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 October 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 15 October 2021. The deadline for submitting written statements was 5 November 2021.

The oral hearing was held on 22 November 2021.

By letter dated 23 November 2021, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 10 December 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and 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 21 December 2021, and the proposed resolution was approved.

At its session on 6 January 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	26 February 2019	Determination of the appropriate comparator therapy
Working group Section 35a	16 November 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	22 November 2021 23 November 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	30 November 2021 14 December 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	21 December 2021	Concluding discussion of the draft resolution
Plenum	6 January 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 6 January 2022

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

Prof. Hecken