Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
rADAMTS13 (ADAMTS13 deficiency in congenital thrombotic thrombocytopenic purpura (cTTP))

of 20 February 2025

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 all reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of rare diseases (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, 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, No. 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 € 30 million in 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 according to 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 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). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the 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 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 the 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 turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient rADAMTS13 on 1 September 2024 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. 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 29 August 2024.

rADAMTS13 as enzyme replacement therapy (ERT) for the treatment of ADAMTS13 deficiency in children and adults with congenital thrombotic thrombocytopenic purpura (cTTP) is approved as a medicinal product for the treatment of rare diseases in accordance with 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 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 on the basis of the approval studies by the G-BA.

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 2 December 2024 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 adopted its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G24-22) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the 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 rADAMTS13.

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of rADAMTS13 (Adzynma) in accordance with the product information

ADZYNMA is an enzyme replacement therapy (ERT) indicated for the treatment of ADAMTS13 deficiency in children and adult patients with congenital thrombotic thrombocytopenic purpura (cTTP). ADZYNMA can be used for all age groups.

Therapeutic indication of the resolution (resolution of 20 February 2025):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

Body of evidence:

<u>281102 study</u>

For the benefit assessment, the pharmaceutical company submitted the results of the 281102 study. The 281102 study is a multi-centre, randomised, controlled, open-label, two-phase cross-over study followed by a single-arm extension phase to investigate the efficacy and safety of rADAMTS13 as a prophylactic and on-demand treatment for patients with cTTP.

In the 281102 study, rADAMTS13 was compared with a standard therapy (SoC - Standard of Care, plasma-based therapy).

The study consists of 3 consecutive periods of 6 months each. In period 1, patients received treatment according to the allocated intervention. In period 2, the patients switched treatment to the alternative intervention. In period 3, all subjects were then treated with rADAMTS13. After completion of period 3, the study participants could move onto the single-arm 3002 extension study. The comparative RCT phases (periods 1 and 2) for prophylactic treatment are used for the benefit assessment.

Patients from the on-demand cohort were able to move onto the prevention cohort after treatment and resolution of the acute event. Data on acute treatment in the on-demand cohort were not used by the pharmaceutical company in the dossier, as these analyses are considered to be less significant for the benefit assessment due to the small sample size (N=6) and the short treatment duration.

The dosage and treatment duration with rADAMTS13 was in accordance with the product information.

A total of 48 subjects were randomised into the overall prevention cohort (N=22 for rADAMTS13 treatment, N=26 for SoC treatment).

Patients aged 0 to 70 years with a documented diagnosis of severe hereditary ADAMTS13 deficiency and ADAMTS13 activity < 10% were enrolled in the 281102 study.

Acute TTP events under prophylactic treatment represent the primary endpoint of the 281102 study.

The study initiated in October 2017 was conducted in study sites in Europe, USA and Japan. The study was completed on 30 May 2024.

The second non-pre-specified data cut-off from 11 August 2023 required by the EMA was used for the benefit assessment. A study report for the final data cut-off on 30 May 2024 was not yet available at the time of dossier submission. However, the observation of periods 1 and 2 had been completed for all subjects included in the prevention cohort as early as the data cut-off from 11 August 2023, which is why it is assumed that the final data cut-off does not provide any additional insight into the comparative observation period compared to the data cut-off from 11 August 2023.

In summary, the additional benefit of rADAMTS13 is assessed as follows:

The pharmaceutical company did not use data on acute treatment from the 281102 study in the dossier, as these analyses were considered to be less significant for the benefit assessment due to the small sample size (N=6) and the short treatment duration. This estimate is shared by the G-BA.

Thus, the available data from the 281102 study only allow statements on the additional benefit of rADAMTS13 for adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) who receive rADAMTS13 as a prophylactic treatment. The G-BA therefore considers a subdivision of the patient population with regard to the acute or prophylactic treatment with rADAMTS13 to be appropriate:

a) Adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) receiving rADAMTS13 as prophylactic treatment

   Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification

b) Adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) receiving rADAMTS13 for acute treatment

   Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification

Justification:

a) Adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) receiving rADAMTS13 as prophylactic treatment

Mortality

Deaths

Deaths were collected in the 281102 study within the safety endpoints from the first dose of study medication to the end of the study or study discontinuation.

No deaths have occurred in the course of the study.

The endpoint "deaths" is irreversible and therefore cannot be meaningfully analysed in a crossover study design. The present study design is therefore unsuitable for comparing the number of deaths between the treatment arms.

Morbidity

Acute cTTP events

The incidence of acute cTTP events during prophylactic treatment of cTTP is the primary endpoint of the 281102 study.

Acute cTTP events were defined as the simultaneous occurrence of thrombocytopenia, as measured by platelet count, and microangiopathic haemolytic anaemia (MAHA), as measured by an increase in lactate dehydrogenase (LDH).

As a result, there was no statistically significant difference between treatment with rADAMTS13 and treatment with standard of care (SoC) for the incidence of acute cTTP events during prophylactic treatment of cTTP.

The platelet count and LDH are laboratory parameters and are therefore not directly patient-relevant. In addition, there is no validation of the incidence of acute cTTP events as a surrogate parameter for patient-relevant endpoints.

The occurrence of acute cTTP events can be an important therapy management parameter and is presented additionally.

Subacute cTTP events

Subacute cTTP events in the 281102 study were defined as the simultaneous occurrence of at least 2 criteria (thrombocytopenia (measured by platelet count), MAHA (measured by an increase in LDH) and an organ-specific sign or symptom), with at least one criterion fulfilling the definition of thrombocytopenia or MAHA.

For the endpoint "subacute cTTP events", there was a statistically significant difference in favour of rADAMTS13 compared to SoC.

The endpoint "subacute cTTP events" is a composite endpoint that includes both symptomatic and non-symptomatic components. According to the present operationalisation, the change in the laboratory parameters mentioned (platelet count, LDH) alone may be sufficient to be estimated as a subacute cTTP event. These laboratory parameters are not directly patient-relevant endpoints. The pre-specified symptomatic components are considered patient-relevant. In the dossier and at the oral hearing, the pharmaceutical company explained that all subacute cTTP events were also associated with symptoms in each case. However, a review of the individual subacute events that occurred in the benefit assessment evaluation did not show that each subacute event was associated with a cTTP-specific symptom. Furthermore, it is uncertain which organ-specific symptoms were included in the analyses in this study, as these were not mentioned in full. It therefore remains unclear which other events were estimated as part of this endpoint.

As a result, the endpoint of subacute cTTP events is therefore not considered patient-relevant in the present operationalisation and is only presented additionally.

Neurological symptoms

Neurological symptoms included the occurrence of headache, confusion, memory problems, irritability, paraesthesia, dysarthia, dysphonia, visual disorders, focal or generalised motor symptoms including seizures.

Significant uncertainties arise from the fact that the symptoms are not conclusively named and it remains unclear which other symptoms were estimated as part of this endpoint.

As a result, there was no statistically significant difference between rADAMTS13 and SoC in the endpoint of neurological symptoms.

Quality of life

Health-related quality of life was assessed in an age-appropriate manner using the SF-36 (Short Form-36 Health Survey) and PedsQL (Paediatric Quality of Life Inventory) instruments.

With reference to the low return rates, the pharmaceutical company did not provide any data on health-related quality of life. Across all periods, the return rates of the SF-36 were slightly below 70% and those of the PedsQL significantly below 70%.

This means that no data are available and it is not possible to assess the effect of rADAMTS13 on health-related quality of life.

Side effects

All adverse events that occurred after the first administration of the study medication up to 30 days after the end of the study or study discontinuation were taken into account in the study. The safety analysis thus also included the data from PK-I, the data from the subjects who move onto the prevention cohort after completing the on-demand phase, as well as the additional data from the on-demand phase, so that the safety population comprised 49 subjects. No additional analyses excluding disease-related events were presented for the benefit assessment. When interpreting the results, it should therefore be noted that the reported AEs also partly reflect events of the underlying disease.

Adverse events (AEs) in total

In the 281102 study, 86% of patients in the intervention arm experienced an adverse event, compared to 90% of patients in the comparator arm. The results were only presented additionally.

Serious adverse events (SAE)

For the endpoint of SAE, the safety population of the study showed a statistically significant difference to the advantage of rADAMTS13 compared to SoC.

For the endpoint of SAE, an overall advantage of rADAMTS13 over SoC is assumed.

However, the assessment of the extent of this advantage is subject to relevant uncertainties. These result in particular from the protocol-compliant collection of TTP manifestations (events

of the underlying disease) as AEs in conjunction with the overall low number of events observed in the study.

Severe AEs and therapy discontinuation due to AEs.

For the endpoints "severe adverse events" and "therapy discontinuation due to AEs", there was no statistically significant difference between the treatment arms in the safety population in each case.

Adverse events of special interest

No AEs of special interest were pre-specified.

Overall assessment

For the assessment of the additional benefit of rADAMTS13 for the treatment of adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) who receive rADAMTS13 as prophylactic treatment, results are available from the 281102 study for the endpoint categories of mortality, morbidity and side effects compared to Standard of Care (SoC).

In the course of the study, there were no deaths with regard to the endpoint category of mortality.
The endpoint "deaths" is irreversible and therefore cannot be meaningfully analysed in a crossover study design. The present study design is therefore unsuitable for comparing the number of deaths between the treatment arms.

The analyses presented for the endpoint of subacute cTTP events in the endpoint category of morbidity are assessed to be non-patient-relevant in the present operationalisation because it could not be shown that every event in the study was associated with a cTTP-specific symptom. According to the present operationalisation, the change in the corresponding laboratory parameters alone could be sufficient to be estimated as a subacute cTTP event. These laboratory parameters are not directly patient-relevant endpoints. In addition, there was no statistically significant difference between the treatment groups in the morbidity category for the endpoint of neurological symptoms in the study.

No data are available on health-related quality of life.

The results on side effects show a statistically significant difference in favour of rADAMTS13 compared to SoC for the endpoint of SAE. Overall, an advantage of rADAMTS13 over SoC is assumed. However, the estimation of this advantage is subject to relevant uncertainties.

In the overall assessment, the G-BA classifies the extent of the additional benefit of rADAMTS13 for the treatment of adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) who receive rADAMTS13 as prophylactic treatment as non-quantifiable since the scientific data does not allow quantification.

Significance of the evidence

The results of an RCT are available for the present assessment.

The risk of bias across endpoints is estimated to be high at study level due to the lack of blinding.

The risk of bias of the relevant endpoints for the benefit assessment is assessed as high for the following reasons:

The pharmaceutical company states in the statement that they calculated p values for all endpoints using the McNemar test. The McNemar test is considered suitable for evaluation of the dichotomous endpoints in the study due to the consideration of the correlation of the data, and the p values are used for the benefit assessment. However, there are uncertainties regarding these p values due to the lack of information on the actual specification of the test and the lack of comprehensible information on how they were actually calculated.

In addition, the pharmaceutical company subsequently submitted relative risks (RR) as effect estimators for all endpoints together with correlated and uncorrelated 95% confidence intervals (CI) in the written statement procedure. However, no information is available on the methodology used to calculate these relative risks together with the respective 95% CIs. Only data on correlation is available for the 95% CI. The relative risks and the associated 95% CI are considered suitable for the assessment. However, the lack of information on their calculation results in relevant uncertainties in the present study design.

The significance of the evidence is therefore classified in the "hint" category.

b) Adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) receiving rADAMTS13 for acute treatment

The pharmaceutical company did not use data on acute treatment from the 281102 study in the dossier, as these analyses were considered to be less significant for the benefit assessment due to the small sample size (N=6) and the short treatment duration. This estimate is shared by the G-BA.

No data are available for the assessment of the additional benefit of rADAMTS13 for the treatment of adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) who receive rADAMTS13 for acute treatment.

In the overall assessment, a hint for a non-quantifiable additional benefit is identified since the scientific data basis does not allow quantification.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Adzynma" with the active ingredient "rADAMTS13".

Adzynma was approved under "exceptional circumstances" as an orphan drug.

rADAMTS13 is approved for the treatment of ADAMTS13 deficiency in children and adults with congenital thrombotic thrombocytopenic purpura (cTTP). ADZYNMA can be used for all age groups.

In the therapeutic indication to be considered, 2 patient groups were distinguished:

a) Adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) receiving rADAMTS13 as prophylactic treatment

b) Adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) receiving rADAMTS13 for acute treatment

a) Adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) receiving rADAMTS13 as prophylactic treatment

For the assessment of the additional benefit of rADAMTS13 for the treatment of adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) who receive rADAMTS13 as prophylactic treatment, results are available from the 281102 study for the endpoint categories of mortality, morbidity and side effects compared to Standard of Care (SoC).

In the course of the study, there were no deaths with regard to the endpoint category of mortality.
The endpoint "deaths" is irreversible and therefore cannot be meaningfully analysed in a crossover study design. The present study design is therefore unsuitable for comparing the number of deaths between the treatment arms.

The analyses presented for the endpoint of subacute cTTP events in the endpoint category of morbidity are assessed to be non-patient-relevant in the present operationalisation because it could not be shown that every event in the study was associated with a cTTP-specific symptom. According to the present operationalisation, the change in the corresponding laboratory parameters alone could be sufficient to be estimated as a subacute cTTP event. These laboratory parameters are not directly patient-relevant endpoints. In addition, there was no statistically significant difference between the treatment groups in the morbidity category for the endpoint of neurological symptoms in the study.

No data are available on health-related quality of life.

The results on side effects show a statistically significant difference in favour of rADAMTS13 compared to SoC for the endpoint of SAE. Overall, an advantage of rADAMTS13 over SoC is assumed. However, the estimation of this advantage is subject to relevant uncertainties.

In the overall assessment, the G-BA classifies the extent of the additional benefit of rADAMTS13 for the treatment of adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) who receive rADAMTS13 as prophylactic treatment as non-quantifiable since the scientific data does not allow quantification.

The reliability of data of the additional benefit identified is classified in the "hint" category.

In the overall assessment, a hint for a non-quantifiable additional benefit is identified since the scientific data basis does not allow quantification.

b) Adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) receiving rADAMTS13 for acute treatment

The pharmaceutical company did not use data on acute treatment from the 281102 study in the dossier, as these analyses were considered to be less significant for the benefit assessment due to the small sample size (N=6) and the short treatment duration. This estimate is shared by the G-BA.

No data are available for the assessment of the additional benefit of rADAMTS13 for the treatment of adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) who receive rADAMTS13 for acute treatment.

In the overall assessment, a hint for a non-quantifiable additional benefit is identified since the scientific data basis does not allow quantification.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA bases its resolution on the information from the dossier of the pharmaceutical company.

The pharmaceutical company has calculated the number of patients in the SHI target population using two derivation steps, which comprise the determination of a prevalence rate of cTTP in 2022 on the basis of five studies and the subsequent consideration of the SHI percentage.

Overall, the lower limit of the number of patients in the SHI target population stated by the pharmaceutical company is therefore in a plausible size. However, the upper limit could be higher than that set by the pharmaceutical company, as there are also publications that contain higher prevalence figures. Ultimately, it remains unclear which prevalence figure represents a meaningful upper limit. The prevalence of cTTP varies depending on the population under consideration and there are no epidemiological data for cTTP specifically for Germany. There are also uncertainties regarding the transferability of the prevalence data to 2024.

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 Adzynma (active ingredient: rADAMTS13) at the following publicly accessible link (last access: 5 December 2024):

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

Treatment with rADAMTS13 should only be initiated and monitored by specialists who are experienced in the treatment of patients with haematological diseases.

In accordance with the EMA's requirements regarding additional risk minimisation measures, the pharmaceutical company must provide all patients and healthcare professionals who use or prescribe rADAMTS13 with suitable training material, which essentially comprises the information suitable for the respective recipients on how to deal with hypersensitivity reactions that may occur under rADAMTS13 in the use of rADAMTS13 at home.

This medicinal product was approved under “exceptional circumstances”.

The EMA will assess any new information that becomes available on an annual basis, and, if necessary, the summary of product characteristics will be updated.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 February 2025).

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus (2021 for adults or 2017 for children under 1

year) – body measurements of the population" were used as a basis (average body weight of adults: 77.7 kg and average body weight of children under 1 year: 7.6 kg)[2].

a) Adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) receiving rADAMTS13 as prophylactic treatment

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				
rADAMTS13	Once every 14 days (prophylactic therapy for children) to once every 14 days (prophylactic therapy for adults)	26.1[3]	1	26.1

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
rADAMTS13	Prophylactic therapy 40 I.U./kg BW once every 14 days	Prophylactic therapy for children 304 I.U. every 2 weeks Prophylactic therapy for adults 3108 I.U. every 2 weeks	Prophylactic therapy for children 1 × 304 I.U. every 2 weeks Prophylactic therapy for adults 1 × 3108 I.U. every 2 weeks	Prophylactic therapy for children 304 I.U. on 26.1 days Prophylactic therapy for adults 3108 I.U. on 26.1 days	7,934.4 I.U. (26.1 * 304 I.U.) to 81,118.8 I.U. (26.1 * 3,108 I.U.)

[2] Federal Health Reporting. Average body measurements of the population (2021 for adults and 2017 for children under 1 year), www.gbe-bund.de

[3] Lower limit: Number of treatments with rADAMTS13 for prophylactic treatment of children according to PI; upper limit: Number of treatments with rADAMTS13 for prophylactic treatment of adults according to PI

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

a) Adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) receiving rADAMTS13 as prophylactic treatment

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Adzynma 500 I.U.	1 PSI	€ 2,306.82	€ 1.77	€ 128.45	€ 2,176.60
Adzynma 1500 I.U.	1PLI	€ 6,805.13	€ 1.77	€ 385.35	€ 6,418.01
Abbreviations: PSI = powder and solvent for solution for injection					

LAUER-TAXE® last revised: 1 February 2025

b) Adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) receiving rADAMTS13 for acute treatment

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				
rADAMTS13	Once a day for 7 days (on-demand therapy of acute episodes in children) to once a	7[4]	1	7

[4] Lower limit: Number of treatments with rADAMTS13 for the treatment of an acute episode in children according to PI; upper limit: Number of treatments with rADAMTS13 for the treatment of an acute episode in adults according to PI

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	day for 7 days (on-demand therapy of acute episodes in adults)			

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
rADAMTS13	On-demand therapy for the acute episode 40 I.U./kg BW on day 1 20 I.U./kg BW on day 2 15 I.U./kg BW on days 3 to 7	On-demand therapy for acute episodes in children 304 I.U. on day 1 152 I.U. on day 2 114 I.U. on days 3 to 7 On-demand therapy for acute episodes in adults 3108 I.U. on day 1 1554 I.U. on day 2 1165.5 I.U. on days 3 to 7	On-demand therapy for acute episodes in children 1 × 304 I.U. on day 1 1 × 152 I.U. on day 2 In each case 1 × 114 I.U. on days 3 to 7 On-demand therapy for acute episodes in adults 1 × 3108 I.U. on day 1 1 × 1554 I.U. on day 2 In each case 1 × 1165.5 I.U. on days 3 to 7	On-demand therapy for acute episodes in children 304 I.U. = 1 day 152 I.U. = 1 day In each case 114 I.U. on 5 days On-demand therapy for acute episodes in adults 3108 I.U. = 1 day 1554 I.U. = 1 day	1,026 (304 + 152 + 5*114) I.U. to 10,489.5 (3,108 + 1,554 + 5*1,165.5)

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
				In each case 1165.5 I.U. on 5 days	

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

b) Adults and children with congenital thrombotic thrombocytopenic purpura (cTTP) receiving rADAMTS13 for acute treatment

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Adzynma 500 I.U.	1 PSI	€ 2,306.82	€ 1.77	€ 128.45	€ 2,176.60
Adzynma 1500 I.U.	1PLI	€ 6,805.13	€ 1.77	€ 385.35	€ 6,418.01
Abbreviations: PSI = powder and solvent for solution for injection					

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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.

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

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active

ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults and children with congenital thrombotic thrombocytopenic purpura (cTTP)

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:

Product information for rADAMTS13 (ADZYNMA); ADZYNMA 500/1500 I.U.: powder and solvent for solution for injection; last revised: August 2024

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

On 29 August 2024, the pharmaceutical company submitted a dossier for the benefit assessment of rADAMTS13 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 2 December 2024 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 23 December 2024.

The oral hearing was held on 6 January 2025.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 30 January 2025.

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 11 February 2025, and the draft resolution was approved.

At its session on 20 February 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	26 November 2024	Information of the benefit assessment of the G-BA
Subcommittee on Medicinal Products	6 January 2025	Information on statements received, conduct of the oral hearing
Working group Section 35a	14 January 2025 4 February 2025	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	11 February 2025	Concluding discussion of the draft resolution
Plenum	20 February 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 20 February 2025

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

Prof. Hecken