Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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

At its session on 20 February 2025, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient rADAMTS13 as follows:

rADAMTS13

Resolution of: 20 February 2025
Entry into force on: 20 February 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx
SHI

Therapeutic indication (according to the marketing authorisation of 1 August 2024):

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 therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

rADAMTS13 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 on orphan drugs. In accordance with 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.

The G-BA determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5 Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5 Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

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

Extent of the additional benefit and significance of the evidence of rADAMTS13:

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

Extent of the additional benefit and significance of the evidence of rADAMTS13:

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

Study results according to endpoints:[1]

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.c.	The data are not assessable.
Morbidity	↔	No relevant difference for the benefit assessment.
Health-related quality of life	∅	No data available.
Side effects	↑	Advantage in the endpoint of SAE.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

281102 study: multicentre, randomised, controlled, open-label, two-phase cross-over study],

rADAMTS13 **vs** Standard of Care (SoC) (includes FFP (Fresh Frozen Plasma) (IV), pooled S/D (Solvent/Detergent)-treated plasma (IV) or factor VIII: von Willebrand factor concentrates (IV))

Mortality

Endpoint	rADAMTS13		SoC		rADAMTS13 vs SoC
	N[c]	*Patients with event n (%)*	N[c]	*Patients with event n (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
Mortality					
Deaths[d]	No suitable data available.				

[1] Data from the dossier assessment of the G-BA (published on 2. Dezember 2024), and from the amendment to the dossier assessment from 30 January 2025, unless otherwise indicated.

Morbidity

Endpoint	rADAMTS13		SoC		rADAMTS13 vs SoC
	N[e]	*Patients with event n (%)*	N[e]	*Patients with event n (%)*	RR [95% CI][g] p value[h] Absolute difference (AD)[a]
Symptomatology					
Neurological symptoms	45	4 (9)	45	7 (15)	0.86 [0.49; 1.51] 0.76
Acute cTTP events (presented additionally)[b]					
	45	1 (2)	45	1 (2)	1.00 [0.25; 4.00] 1.0
Endpoint	**rADAMTS13**		**SoC**		**rADAMTS13 vs SoC**
	N[e]	*Patients with event n (%)*	N[e]	*Patients with event n (%)*	RR [95% CI][g] p value[h] Absolute difference (AD)[a]
Subacute cTTP events (presented additionally)					
	45	1 (2)	45	6 (13)	0.17 [0.04; 0.67] 0.006

Health-related quality of life

No data available.

Side effects[f]

Endpoint **MedDRA system organ classes/ preferred terms/ AEs of special interest**	**rADAMTS13**		**SoC**		rADAMTS13 vs SoC
	N[c]	*Patients with event n (%)*	N[c]	*Patients with event n (%)*	RR [95% CI][g] p value[h]
Total adverse events (presented additionally)	49	42 (86)	49	44 (90)	-
Serious adverse events (SAE)	49	1 (2)	49	8 (16)	0.13 [0.03; 0.50] 0.0005
Severe adverse events	49	4 (8)	49	8 (16)	0.50 [0.25; 1.00] 0.08
Therapy discontinuation due to adverse events	49	0 (0)	49	1 (2)	n.a. [n.a.; n.a.] 0.50
Endpoint **MedDRA system organ classes/ preferred terms/ AEs of special interest**	**rADAMTS13**		**SoC**		rADAMTS13 vs SoC
	N[c]	*Patients with event n (%)*	N[c]	*Patients with event n (%)*	RR [95% CI][g] p value[h]
Adverse events of any severity according to MedDRA (with an incidence ≥ 10% under rADAMTS13 and SoC treatment; SOC and PT)					
Infections and infestations, SOC	49	25 (51)	49	22 (45)	1.14 [0.86; 1.50] 0.45
COVID-19, PT	49	5 (10)	49	3 (6)	1.67 [0.90; 3.10] 0.22
Nasopharyngitis, PT	49	7 (14)	49	6 (12)	1.17 [0.69; 1.97] 0.77
Upper respiratory tract infection, PT	49	6 (12)	49	3 (6)	2.00 [1.14; 3.52] 0.03

Blood and lymphatic system disorders, SOC	49	9 (18)	49	12 (24)	0.75 [0.47; 1.19] 0.31
Thrombocytopenia, PT	49	5 (10)	49	9 (18)	0.56 [0.30; 1.03] 0.10
Immune system disorders, SOC	49	1 (2)	49	5 (10)	0.20 [0.05; 0.80] 0.02
Metabolism and nutrition disorders, SOC	49	6 (12)	49	4 (8)	1.50 [0.85; 2.64] 0.29
Nervous system disorders, SOC	49	18 (37)	49	14 (29)	1.29 [0.93; 1.78] 0.18
Headache, PT	49	13 (27)	49	11 (22)	1.18 [0.80; 1.74] 0.52
Endpoint MedDRA system organ classes/ preferred terms/ AEs of special interest	**rADAMTS13**		**SoC**		rADAMTS13 vs SoC
	N[c]	*Patients with event n (%)*	N[c]	*Patients with event n (%)*	RR [95% CI][g] p value[h]
Migraine, PT	49	6 (12)	49	2 (4)	3.00 [1.35; 6.68] 0.008
Vascular disorders, SOC	49	7 (14)	49	4 (8)	1.75 [1.04; 2.95] 0.03
Respiratory, thoracic and mediastinal disorders, SOC	49	12 (24)	49	9 (18)	1.33 [0.89; 1.99] 0.24
Gastrointestinal disorders, SOC	49	18 (37)	49	16 (33)	1.13 [0.81; 1.56] 0.60
Abdominal pain, PT	49	4 (8)	49	6 (12)	0.67 [0.33; 1.33] 0.39
Diarrhoea, PT	49	7 (14)	49	2 (4)	3.50 [1.53; 8.01] 0.002

Nausea, PT	49	5 (10)	49	3 (6)	1.67 [0.90; 3.10] 0.22
Vomiting, PT	49	5 (10)	49	6 (12)	0.83 [0.45; 1.55] 0.56
Skin and subcutaneous tissue disorders, SOC	49	7 (14)	49	12 (24)	0.58 [0.35; 0.98] 0.04
Pruritus, PT	49	2 (4)	49	5 (10)	0.40 [0.15; 1.07] 0.11
Endpoint **MedDRA system organ classes/ preferred terms/ AEs of special interest**	**rADAMTS13**		**SoC**		rADAMTS13 vs SoC
	N[c]	*Patients with event n (%)*	N[c]	*Patients with event n (%)*	RR [95% CI][g] p value[h]
Urticaria, PT	49	0 (0)	49	7 (14)	n.a. [n.a.; n.a.] 0.0002
Musculoskeletal and connective tissue disorders, SOC	49	7 (14)	49	10 (20)	0.70 [0.41; 1.18] 0.26
General disorders and administration site conditions, SOC	49	11 (22)	49	14 (29)	0.79 [0.52; 1.19] 0.34
Fatigue, PT	49	2 (4)	49	7 (14)	0.29 [0.11; 0.76] 0.01
Investigations, SOC	49	5 (10)	49	6 (12)	0.83 [0.45; 1.55] 0.56
Injury, poisoning and procedural complications, SOC	49	6 (12)	49	11 (22)	0.55 [0.31; 0.96] 0.03

a. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
b. Primary endpoint of the 281102 study
c. Safety population: Number of patients refers to the study period PK-I + period 1+2. The number corresponds to the number of subjects from the prophylactic cohort, subjects who

switched from the on-demand cohort to the prevention cohort and additional data from the on-demand phase.

d. The present study design of the cross-over study is unsuitable for collecting deaths in the course of the study.
e. Number of randomised subjects in the prevention cohort refers to the study period of period 1+2
f. The study's own criteria were used for severity grading.
g. Calculated post hoc: No data available for statistical evaluation. According to the information provided by the pharmaceutical company in their statement, correlation of the data was taken into account in the calculation of the 95% CI.
h. Calculated post hoc: According to the information provided by the pharmaceutical company in their statement, calculated using the McNemar test (correlated). There is a lack of information on the specific test used.

Abbreviations used:
AD = absolute difference; n.d.: no data available; CI = confidence interval; N = number of patients evaluated; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not applicable; PT = preferred term; RR = relative risk; SoC = standard of care; SOC = system organ class; (S)AE = (serious) adverse event; vs = versus

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: No data available.
n.a.: not assessable

2. Number of patients or demarcation of patient groups eligible for treatment

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

and

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

Approx. 60 to 90 patients

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.

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
rADAMTS13	€ 56,809.26 - € 391,829.38

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2025)

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

c) Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
rADAMTS13	€ 15,236.20 - € 55,697.28

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2025)

Costs for additionally required SHI services: not applicable

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

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

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.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. 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.

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 20 February 2025.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 20 February 2025

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

Prof. Hecken