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)
Garadacimab (hereditary angioedema, prophylaxis, ≥ 12 years)

of 21 August 2025

At their session on 21 August 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 Garadacimab as follows:

Garadacimab

Resolution of: 21 August 2025
Entry into force on: 21 August 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 10 February 2025):

ANDEMBRY is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

Therapeutic indication of the resolution (resolution of 21 August 2025):

See therapeutic indication according to marketing authorisation.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

Adolescents aged 12 and older and adults with recurrent attacks of hereditary angioedema

Appropriate comparator therapy for garadacimab for routine prevention:

- Routine prevention with a C1 esterase inhibitor or lanadelumab or berotralstat

Extent and probability of the additional benefit of garadacimab compared to berotralstat:

Hint for a considerable additional benefit

Study results according to endpoints:[1]

Adolescents aged 12 and older and adults with recurrent attacks of hereditary angioedema

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑	Advantage in the monthly rate of HAE attacks. Advantage in health status.
Health-related quality of life	↑	Advantage in health-related quality of life.
Side effects	↔	No relevant difference for the benefit assessment.
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		

Indirect comparison:

Garadacimab (VANGUARD study) vs berotralstat (APeX-2 and APeX-J studies) via the bridge comparator placebo

Mortality

Endpoint Comparison Study	Garadacimab or berotralstat		Placebo		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
Mortality/overall mortality[b]					
Garadacimab vs placebo VANGUARD	39	0 (0)	25	0 (0)	–
Berotralstat vs placebo APeX-2 APeX-J	40 7	0 (0) 0 (0)	40 6	0 (0) 0 (0)	– –
Indirect comparison via bridge comparators[c]**:**	not presented				

[1] Data from the dossier assessment of the IQWiG (A25-41) and from the addendum (A25-94), unless otherwise indicated.

Morbidity

Endpoint Comparison Study	Garadacimab or berotralstat		Placebo		Group difference
	N	Average monthly rate [95% CI][d]	N	Average monthly rate [95% CI][d]	Rate ratio [95% CI] p value[d]
HAE attacks monthly rate[e, f]					
Garadacimab vs placebo VANGUARD	39	0.22 [0.11; 0.46]	25	2.07 [1.50; 2.86]	0.11 [0.05; 0.24] < 0.001
Berotralstat vs placebo APeX-2	40	1.33 [n.d.]	39	2.35 [n.d.]	0.56 [0.41; 0.78] < 0.001
APeX-J	7	1.08 [n.d.]	6	2.12 [n.d.]	0.51 [0.33; 0.79] < 0.003
Total[g]					0.54 [0.42; 0.70] < 0.001
Indirect comparison via bridge comparators[c]: Garadacimab vs berotralstat					0.20 [0.09; 0.47] < 0.001
Endpoint **Comparison** **Study**	**Garadacimab or berotralstat**		**Placebo**		**Group difference**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
Attack-free status[e, h]					
Garadacimab vs placebo VANGUARD	39	24 (61.5)	25	0 (0)	31.85 [2.02; 501.25] 0.014
Berotralstat vs placebo APeX-2	40	2 (5.0)	39	1 (2.6)	1.95 [0.18; 20.64] 0.579
APeX-J	7	0 (0)	6	0 (0)	0.88 [0.02; 38.59] 0.945
Total[g]					1.56 [0.21; 11.54] 0.664
Indirect comparison via bridge comparators[c]: Garadacimab vs berotralstat					20.42 [0.68; 616.19] 0.083

Endpoint Comparison Study	Garadacimab or berotralstat			Placebo			Group difference
	N[i]	Values at the start of study MV (SD)	Mean change at the end of treatment[j] MV (SD/SE)[k]	N[i]	Values at the start of study MV (SD)	Mean change at the end of treatment[j] MV (SD/SE)[k]	MD [95% CI][k] p value
Activity impairment (WPAI question 6[l])							
Garadacimab vs placebo VANGUARD	37	32.6 (31.9)	n.d.	23	24.5 (26.0)	n.d.	-2.93 [-4.30; -1.55] < 0.001
Berotralstat vs placebo APeX-2	38[m]	3.6 (2.8)	-1.6 (0.4)	36[m]	4.1 (2.8)	-1.2 (0.4)	-0.5 [-1.7; 0.7] 0.406
APeX-J	7	3.3 (2.8)	1.0 (1.0)	6	1.3 (3.3)	-1.0 (1.1)	2.1 [-1.2; 5.4] 0.200
Total[g]							-0.20 [-1.32; 0.93] 0.733
Indirect comparison via bridge comparators[c]: Garadacimab vs berotralstat SMD [95% CI]:							-2.73 [-4.51; -0.95] 0.003 -0.66 [-1.11; -0.22]
Health status (EQ-5D VAS[n])							
Garadacimab vs placebo VANGUARD	38[m]	85.8 (15.7)	6.1 (1.3)	23[m]	82.6 (18.7)	-6.9 (1.7)	14.99 [9.80; 20.18] < 0.001
Berotralstat vs placebo APeX-2	38[m]	82.9 (12.6)	2.7 (1.8)	36[m]	85.2 (10.8)	3.3 (1.8)	-0.6 [-5.8; 4.5] 0.807
APeX-J	7	75.7 (30.61)	8.4 (4.7)	6	80.5 (26.3)	-3.6 (5.1)	12.0 [-3.7; 27.8] 0.120
Total[g]							0.62 [-4.28; 5.51] 0.805
Indirect comparison via bridge comparators[c]: Garadacimab vs berotralstat SMD [95% CI]:							14.37 [7.24; 21.50] < 0.001 0.85 [0.40; 1.29]

Health-related quality of life

Endpoint Comparison Study	Garadacimab or berotralstat			Placebo			Group difference
	N[i]	Values at the start of study MV (SD)	Mean change at the end of treatment[j] MV (SD/SE)[k]	N[i]	Values at the start of study MV (SD)	Mean change at the end of treatment[j] MV (SD/SE)[k]	MD [95% CI][k] p value
Angioedema Quality of Life Questionnaire (AE-QoL[o])							
Total score							
Garadacimab vs placebo VANGUARD	33[m]	38.8 (15.0)	-26.5 (17.9)	20[m]	43.7 (21.4)	-2.2 (19.1)	-25.95 [-35.61; -16.29] 0.001
Berotralstat vs placebo APeX-2	38[m]	43.0 (16.9)	-15.8 (2.7)	36[m]	45.9 (20.1)	-11.0 (2.7)	-4.83 [-12.39; 2.74] 0.207
APeX-J	7	39.5 (24.8)	-17.1 (6.5)	6	40.4 (16.0)	0.1 (7.0)	-17.26 [-38.68; 4.15] 0.103
Total[g]							-6.21 [-13.34; 0.92] 0.088
Indirect comparison via bridge comparators[c]: Garadacimab vs berotralstat						SMD [95% CI]:	-19.74 [-31.75; -7.73] < 0.001 -0.74 [-1.21; -0.27]
Function							
Garadacimab vs placebo VANGUARD	33[m]	43.2 (21.0)	-35.8 (23.2)	20[m]	42 (26.0)	1.9 (29.6)	–
Berotralstat vs placebo APeX-2	38[m]	47.1 (21.0)	-22.0 (3.4)	36[m]	45.3 (24.1)	-13.0 (3.5)	–
APeX-J	7	42.0 (28.3)	-14.8 (7.0)	6	32.3 (18.3)	-1.5 (7.5)	–

Fatigue/ mood							
Garadacimab vs placebo VANGUARD	33[m]	34.6 (19.4)	-21.1 (22.9)	20[m]	42.3 (28.0)	-5.8 (27.1)	–
Berotralstat vs placebo APeX-2	38[m]	38.5 (19.3)	-12.7 (3.3)	36[m]	44.5 (23.2)	-10.5 (3.3)	–
APeX-J	7	21.4 (15.5)	-3.2 (7.2)	6	32.5 (18.1)	2.9 (7.8)	–
Anxiety/ shame							
Garadacimab vs placebo VANGUARD	33[m]	44.2 (20.1)	-28.0 (24.1)	20[m]	51.5 (24.2)	-2.5 (18.6)	–
Berotralstat vs placebo APeX-2	38[m]	47.9 (22.9)	-16.2 (3.5)	36[m]	51.5 (26.1)	-11.2 (3.5)	–
APeX-J	7	57.1 (33.1)	-32.6 (7.6)	6	61.8 (25.6)	-4.4 (8.2)	–
Nutrition							
Garadacimab vs placebo VANGUARD	33[m]	23.9 (20.3)	-16.7 (23.3)	20[m]	26.7 (30.0)	-0.6 (16.5)	–
Berotralstat vs placebo APeX-2	38[m]	31.6 (24.0)	-10.0 (3.2)	36[m]	34.0 (25.0)	-7.3 (3.3)	–
APeX-J	7	26.8 (29.3)	-4.3 (8.6)	6	12.5 (15.8)	2.9 (9.3)	–

Side effects

Endpoint Comparison Study	Garadacimab or berotralstat		Placebo		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
Total adverse events (AEs) *(presented additionally)*					
Garadacimab vs placebo VANGUARD	39	25 (64.1)	25	15 (60.0)	–
Berotralstat vs placebo APeX-2 APeX-J	40 7	34 (85.0) 7 (100)	40 6	30 (76.9) 6 (100)	– –
Serious adverse events (SAE)					
Garadacimab vs placebo VANGUARD	39	1 (2.6)	25	0 (0)	1.95 [0.08; 46.07] 0.679
Berotralstat vs placebo APeX-2	40	0 (0)	39	3 (7.7)	0.14 [0.01; 2.61] 0.188
APeX-J	7	0 (0)	6	0 (0)	–
Indirect comparison via bridge comparators[c]: Garadacimab vs berotralstat					14.03 [0.19; 1065.76] 0.232
Severe adverse events no suitable data for indirect comparison[p]					
Therapy discontinuation due to adverse events					
Garadacimab vs placebo VANGUARD	39	0 (0)	25	0 (0)	–
Berotralstat vs placebo APeX-2	40	1 (2.5)	39	1 (2.6)	0.98 [0.06; 15.05] 0.986
APeX-J	7	0 (0)	6	1 (16.7)	0.29 [0.01; 6.07] 0.426
Total[g]					0.57 [0.07; 4.34] n.d.
Indirect comparison via bridge comparators[c]:				not presented	

a. Calculation using the fourfold table: in the case of 0 events in a study arm, the correction factor 0.5 was used in both study arms when calculating effect and CI.
b. The results on overall mortality are based on the data on fatal AEs.
c. Indirect comparison according to Bucher.
d. VANGUARD study: Poisson model stratified by the observed HAE attack rate during the run-in period (1 to < 3 HAE attacks/month and ≥ 3 HAE attacks/month).
APeX-2 and APeX-J studies: negative binomial model; the covariate HAE attack rate at baseline confirmed by the principal investigator was taken into account. The logarithm of the treatment duration was used as an offset variable.
e. VANGUARD and APeX-2 studies: HAE attacks confirmed by the principal investigator;
APeX-J study: HAE attacks confirmed by the independent expert.
f. In the VANGUARD study, one month was defined as 30.4375 days, in the APeX-2 and APeX-J studies as 28 days.
g. Meta-analysis using a fixed-effects model (inverse variance method).
h. Reduction in the number of HAE attacks by 100% during the treatment period compared to the run-in phase.
i. Number of patients who were taken into account in the effect estimation; the values at the start of the study can be based on other patient numbers.
j VANGUARD study: week 26; APeX-2 and APeX-J studies: week 24:
k. Unless otherwise stated: VANGUARD study: MV (SD) and MD [95% CI]: MMRM model adjusted for the value at baseline, visit and the interaction term from visit and treatment. The effect represents the difference in changes (compared to the baseline value) between treatment groups at week 26. APeX-2 and APeX-J studies: MV (SE) and MD [95% CI]: MMRM model adjusted for baseline value, HAE attack rate at baseline, visit and the interaction term from visit and treatment, patient ID was included as a random variable in the model. The effect represents the difference in changes (compared to the baseline value) between treatment groups at week 24.
l. Lower (decreasing) values mean better symptomatology; negative effects (intervention minus comparison) mean an advantage for the intervention (scale range: 0 to 10 points; in the VANGUARD study, the values are given in per cent).
m. Number of patients with values at the end of treatment; it is unclear how many patients were included in the model.
n. Higher (increasing) values mean better symptomatology; positive effects (intervention minus comparison) mean an advantage for the intervention (scale range: 0 to 100 points).
o. Lower values mean better health-related quality of life; negative effects (intervention minus comparison) mean an advantage for the intervention (scale range: 0 to 100 points).
p. For an explanation, see the description in the justification and Section I 4.1 of IQWiG's dossier assessment.

AE-QoL: Angioedema Quality of Life Questionnaire; HAE: hereditary angioedema; n.d.: no data available; CI: confidence interval; MD: mean difference; MMRM: mixed model for repeated measures; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; RR: relative risk; SD: standard deviation; SE: standard error; SMD: standardised mean difference; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; WPAI: Work Productivity and Activity Impairment

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

Adolescents aged 12 and older and adults with recurrent attacks of hereditary angioedema

Approx. 140 – 440 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 Andembry (active ingredient: garadacimab) at the following publicly accessible link (last access: 4 July 2025):

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

Treatment with garadacimab should only be initiated and monitored by specialists who are experienced in the treatment of patients with hereditary angiooedema.

According to the product information, therapy discontinuation should be considered in patients with normal C1-INH-HAE (nC1-INH) who have shown insufficient reduction in attacks after 3 months of treatment with garadacimab.

4. Treatment costs

Annual treatment costs:

Adolescents aged 12 and older and adults with recurrent attacks of hereditary angioedema

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Garadacimab	€ 260,672.08
Appropriate comparator therapy:	
C1 esterase inhibitor	€ 190,355.94 – € 253,738.42
Lanadelumab	€ 131,816.71 – € 264,647.39
Berotralstat	€ 181,327.98

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

Adolescents aged 12 and older and adults with recurrent attacks of hereditary angioedema

- No medicinal product with new active ingredients that can be used in a combination therapy that 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.

6. Percentage of study participants at study sites within the scope of SGB V in accordance with Section 35a, paragraph 3, sentence 5 SGB V

The medicinal product Andembry is a medicinal product placed on the market from 1 January 2025.

The percentage of study participants in the clinical studies of the medicinal product conducted or commissioned by the pharmaceutical company in the therapeutic indication to be assessed who participated at study sites within the scope of SGB V (German Social Security Code) is ≥ 5% of the total number of study participants.

The clinical studies of the medicinal product in the therapeutic indication to be assessed were therefore conducted to a relevant extent within the scope of SGB V.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 21 August 2025.

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

Berlin, 21 August 2025

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

Prof. Hecken