Gemeinsamer Bundesausschuss

Angiotensin II Acetate

Resolution of: 6 January 2022 valid until: unlimited
Entry into force on: 6 January 2022
Federal Gazette, BAnz AT 09 03 2022 B2

Therapeutic indication (according to the marketing authorisation of 23 August 2019):

"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 6 January 2022):

see therapeutic indication according to marketing authorisation

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

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

Appropriate comparator therapy:

An optimised standard therapy.

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

Extent and probability of the additional benefit of Angiotensin II Acetate compared to optimised standard therapy:

An additional benefit is not proven.

Study results according to endpoints:[2]

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

[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).
[2] Data from the dossier assessment of the IQWiG (A21-95) and from the addendum (A21-147), unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↔	No relevant difference for the benefit assessment.
Health-related quality of life	∅	No data available.
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
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

ATHOS-3 study: Angiotensin II Acetate vs Placebo (each in addition to vasopressor therapy)[3]

Mortality

Endpoint	Angiotensin II Acetate + optimised standard therapy		Placebo + optimised standard therapy		Intervention vs control
	N[a]	Median survival time in days [95% CI] Patients with event n (%)	N[a]	Median survival time in days [95% CI] Patients with event n (%)	Effect estimator [95% CI] p value[g] Absolute difference (AD)[f]
Overall mortality (day 28)	163	n.a. [19.12; n.a.] 75 (46.0)	158	15.50 [10.03; n.a.] 85 (53.8)	HR = 0.78 [0.57; 1.07]; 0.123

[3] 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.

Morbidity

Endpoint	Angiotensin II Acetate + optimised standard therapy		Placebo + optimised standard therapy		Intervention vs control
	N[a]	Median survival time in days [95% CI] Patients with event n (%)	N[a]	Median survival time in days [95% CI] Patients with event n (%)	Effect estimator [95% CI] p value[g] Absolute difference (AD)[f]
Discharge from the intensive care unit	163	16 [14; 20] 72 (44.2)	158	17 [14; 20] 62 (39.2)	HR = 0.99 [0.71; 1.39]; 0.957
Discontinuation of artificial respiration	No usable data available[b]				
Discontinuation of renal replacement therapy	No usable data available[c]				
MAP response rate[h] (presented additionally)	163	114 (69.9)	158	37 (23.4)	RR = 2.99 [2.21; 4.03]; < 0.001 AD = 46.5%

Health-related quality of life

Endpoint not surveyed.

Side effects

Endpoint	Angiotensin II Acetate + optimised standard therapy		Placebo + optimised standard therapy		Intervention vs control
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	Effect estimator [95% CI] p value[d] Absolute difference (AD)[f]
Adverse events in total					
	163	142 (87.1)	158	145 (91.8)	–
Serious adverse events (SAE)					
	163	99 (60.7)	158	106 (67.1)	RR = 0.91 [0.77; 1.07]; 0.258

Therapy discontinuation due to adverse events					
	163	23 (14.1)	158	34 (21.5)	RR = 0.66 [0.41; 1.06]; 0.085
Specific adverse events					
Embolism and thrombosis events (SMQ, SAEs)	163	9 (5.5)	158	4 (2.5)	RR = 2.18 [0.69; 6.94]; 0.226
Peripheral ischaemia (PT, SAEs)	163	5 (3.1)	158	3 (1.9)	RR = 1.62 [0.39; 6.65]; 0.539
Arrhythmias	No usable data available[e]				

a. mITT population
b. The endpoint is defined as the period between the start of treatment and the end of artificial respiration and evaluations with an observation period of 7 days are available. The results presented by the pharmaceutical company 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. No usable data are available for this endpoint.
c. The endpoint is defined as the time 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. As this percentage is very small, the data do not allow any statements to be made for all patients in the study. Furthermore, the observation period of 7 days is too short to obtain results of any significance. Overall, no usable data are available for this endpoint.
d. IQWiG calculation of RR, 95% CI (asymptotic) and p value (unconditional exact test, CSZ method according to Andrés et al, 1994)
e. The pharmaceutical company does not explain which events are included in this evaluation; thus, it is not possible to distinguish between side effects of the intervention and symptomatology of the underlying disease. The results of the predefined evaluations (SMQ cardiac arrhythmias and SMQ Torsades de Pointes/QT prolongation) are not provided by the pharmaceutical company. Therefore, no usable data are available for the endpoint of arrhythmias.
f. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
g. Cox proportional hazards model and log-rank test,
h. The response rate was defined as the percentage of patients whose MAP was ≥ 75 mm Hg or had increased by ≥ 10 mm Hg from baseline 3 hours after start of treatment.

Abbreviations used:
AD = absolute difference; HR = hazard ratio; CI = confidence interval; MAP = mean arterial pressure; mITT = modified intention to treat; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; pU = pharmaceutical company; RR = relative risk; SMQ = standardised MedDRA query; SAE = serious adverse event; AE = adverse event; vs = versus

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

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

approx. 3,980 to 37,625 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 Giapreza (active ingredient: angiotensin II acetate) at the following publicly accessible link (last access: 1 December 2021):
https://www.ema.europa.eu/en/documents/product-information/giapreza-epar-product-information_en.pdf

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

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Angiotensin II acetate	€ 3,570 - € 7,140[4]
+ Optimised standard therapy	different from patient to patient
Appropriate comparator therapy:	
Optimised standard therapy	different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 December 2021)

Costs for additionally required SHI services: not applicable

[4] Angiotensin II acetate is listed in LAUER-TAXE® as a clinic pack only. 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.