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)
Rezafungin (invasive candidiasis)

of 1 August 2024

At its session on 1 August 2024, 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 Rezafungin as follows:

Rezafungin

Resolution of: 1 August 2024
Entry into force on: 1 August 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 22 December 2023):

Rezzayo is indicated for the treatment of invasive candidiasis in adults.

Therapeutic indication of the resolution (resolution of 1 August 2024):

Therapeutic indication according to marketing authorisation.

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

Rezafungin 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 Federal Joint Committee (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 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).

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

<u>Adults with invasive candidiasis</u>

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

Summary of results for relevant clinical endpoints[1]

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	The data are not assessable
Morbidity	↔	No relevant differences for the benefit assessment
Health-related quality of life	∅	No data available
Side effects	↔	No relevant differences 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

ReSTORE study: double-blind, pivotal, phase III RCT, rezafungin vs caspofungin, treatment phase: ≥ 14 days to ≤ 28 days, follow-up (last visit) day 52 to 59

STRIVE study: double-blind, exploratory, phase II RCT in 2 parts, rezafungin vs caspofungin, treatment phase: ≥ 14 to ≤ 21 days for candidaemia and ≥ 14 to ≤ 28 days for invasive candidiasis, follow-up (last visit): Day 45 to 52 for candidaemia and day 52 to 59 for invasive candidiasis, relevant sub-population: pooled analysis of patients with dosage compliant with the product information from the 2 parts of the study

Mortality

Endpoint Study	Rezafungin		Caspofungin		Rezafungin vs caspofungin
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	HR [95% CI] p value
Overall mortality (presented additionally)					
ReSTORE	93	25 (26.9)	94	24 (25.5)[a)]	1.15 [0.65; 2.04]; 0.64
STRIVE	46	5 (10.9)	61	12 (19.7)	0.56 [0.19; 1.64]; 0.29

1 Data from the dossier assessment of the G-BA (published on 2. Mai 2024), and from the amendment to the dossier assessment from 26 June 2024, unless otherwise indicated.

Endpoint **Study**	Rezafungin		Caspofungin		Rezafungin vs caspofungin
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	HR [95% CI] p value
Overall mortality (presented additionally)					
Pooled population	139	30 (21.6)	155	34 (21.9)	0.97 [0.59; 1.59]; 0.90

Morbidity

Endpoint **Study**	Rezafungin		Caspofungin		Rezafungin vs caspofungin
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value[b)]
Global cure on day 14 (primary endpoint, presented additionally)					
ReSTORE	93	55 (59.1)	94	57 (60.6)	0.98 [0.77; 1.23]; 0.88
Overall response on day 14 (primary endpoint, presented additionally)					
STRIVE	46	35 (76.1)	61	41 (67.2)	1.13 [0.89; 1.44]; 0.39
Subcomponents of the primary endpoints of global cure and overall response:					
Mycological eradication of final follow-up (presented additionally)					
ReSTORE	93	48 (51.6)	94	49 (52.1)	n.d.
STRIVE	46	n.d.	61	n.d.	n.d.
Pooled population	139	n.a.	155	n.a.	n.a.
Clinical response of final follow-up (presented additionally)					
ReSTORE	93	46 (49.5)	94	44 (46.8)	1.06 [0.79; 1.42]; 0.77
STRIVE	46	32 (69.6)	61	38 (62.3)	1.12 [0.85; 1.47]; 0.54
Pooled population	139	78 (56.1)	155	82 (52.9)	1.06 [0.86; 1.31]; 0.64
	N	Patients with event n (%)[d)]	N	Patients with event n (%)[d)]	RR [95% CI][e)]

					p value[f)]
Remission of systemic signs and symptoms on day 14[c)] (presented additionally)					
ReSTORE	93	68 (73.1)	94	66 (70.2)	1.04 [0.87; 1.25]; 0.75
STRIVE	46	33 (71.7)	61	44 (72.1)	1.0 [0.78; 1.26]; 0.97
Pooled population	139	101 (72.7)	155	110 (71.0)	1.02 [0.89; 1.18]; 0.78
Remission of systemic signs and symptoms of final follow-up (presented additionally)					
ReSTORE	93	53 (57.0)	94	52 (55.3)	1.03 [0.80; 1.33] 0.88
STRIVE	46	37 (80.4)	61	48 (78.7)	1.02 [0.84; 1.24]; 0.84
Pooled population	139	90 (64.8)	155	100 (64.5)	1.0 [0.85; 1.89]; 1.0
	N	Average length of stay in days (SD)	N	Average length of stay in days (SD)	Mean difference [95% CI]; p value[g)]
Total number of days in hospital across all referrals					
ReSTORE	93	25.8 (19.44)	94	27.1 (17.61)	-1.24 [-7.32; 4.84]; 0.69
STRIVE	46	25.4 (16.65)	61	31.2 (18.29)	-5.73 [-13.3; 1.57]; 0.12
Total number of days in the intensive care unit across all referrals					
ReSTORE	93	13.9 (18.3)	94	23.1 (19.9)	-9.13 [-21.12; 2.86]; 0.13
STRIVE	46	17.7 (14.6)	61	22.8 (19.5)	-5.12 [-16.13; 5.89]; 0.35

Health-related quality of life

No data on health-related quality of life were collected.

Side effects

Endpoint **Study** *MedDRA system organ classes;* Preferred terms	Rezafungin		Caspofungin		Rezafungin vs caspofungin
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI]; p value[b)]
AE (presented additionally)					
ReSTORE study	98	89 (90.8)	98	83 (84.7)	-
STRIVE study	53	49 (92.5)	68	55 (80.9)	-
Pooled population	151	138 (91.4)	166	138 (83.1)	-
Severe AEs[h)]					
ReSTORE study	98	57 (58.2)	98	59 (60.2)	0.97 [0.77; 1.22]; 0.89
STRIVE study	53	17 (32.1)	68	26 (38.2)	0.84 [0.51; 1.38]; 0.57
Pooled population	151	74 (49.0)	166	85 (51.2)	0.96 [0.77; 1.19]; 0.74
Serious adverse events (SAEs)[i)]					
ReSTORE study	98	55 (56.1)	98	52 (53.1)	1.06 [0.82; 1.37]; 0.77
STRIVE study	53	28 (52.8)	68	29 (42.6)	1.24 [0.85; 1.80]; 0.28
Pooled population	151	83 (55.0)	166	81 (48.8)	1.13 [0.91; 1.39]; 0.31
Therapy discontinuation due to adverse events					
ReSTORE study	98	13 (13.3)	98	11 (11.2)	1.18 [0.56; 2.51]; 0.83
STRIVE study	53	1 (1.9)	68	4 (5.9)	0.32 [0.04; 2.79]; 0.38
Pooled population	151	14 (9.3)	166	15 (9.0)	1.03 [0.51; 2.05]; 1.00

a. In the dossier and the study report, the number of deceased subjects in this study arm was 22, and the number of censored subjects was 72. It is unclear why 24 deceased subjects are listed in the subsequently submitted documents.
b. The p value was collected using Fisher's exact test.
c. Data from module 4.
d. Percentage of subjects with remission of systemic signs and symptoms in relation to the mITT population.
e. Not adjusted for randomisation strata. Own calculation of the RR and two-tailed 95% CI (asymptotic) using the Epitools R package (R package version 0.5-10.1).
f. Own calculation of the p value using an unconditional exact test (z-pooled), validation of the p value using Berger RL. Exact unconditional homogeneity/ independence tests for 2X2 tables [online]. 2005. [Accessed: 16.07.2024]. URL: https://www4.stat.ncsu.edu/~boos/exact/.

g. p value for the difference between the mean values, estimated by linear regression.
h. In the ReSTORE study, AE severity was categorised according to the CTCAE classification, with severe AEs from a CTCAE grade ≥ 3. In the STRIVE study, the severity was categorised by the principal investigators using the predefined categories "mild", "moderate" or "severe". For the pooled population, severe AEs from a CTCAE grade ≥ 3 (ReSTORE study) and "severe" AEs (STRIVE study) were evaluated.
i. SAEs were defined as: AEs that were fatal; required or prolonged hospitalisation; resulted in persistent/ significant disability or incapacity; could be attributed to a congenital anomaly/ birth defect; or as a medically significant event that could have posed a threat or required surgical intervention to prevent any of the events mentioned above.

Abbreviations used:
HR = hazard ratio; n.d.: no data available; CI: confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number of patients with (at least one) event; n.a. = not applicable; n.c. = not calculable; SD = standard deviation; AE = adverse event; SAE = serious adverse event; vs = versus

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

Adults with invasive candidiasis

Approx. 31,800 – 34,600 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 Rezzayo (active ingredient: rezafungin) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 19 July 2024):

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

Treatment with rezafungin should only be initiated and monitored by doctors experienced in therapy of invasive fungal infections.

4. Treatment costs

Annual treatment costs:

Adults with invasive candidiasis

Designation of the therapy	Treatment costs/ patient Infection
Medicinal product to be assessed:	
Rezafungin	€ 8,616.30- € 14,360.50

Costs after deduction of statutory rebates ((LAUER-TAXE®) as last revised: 15 July 2024)

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ Infection	Costs/ patient / Infection
Rezafungin	Preparation of other parenteral solutions	€ 54	2-4	€ 108 - € 216

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 with invasive candidiasis

- 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.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 1 August 2024.

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

Berlin, 1 August 2024

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

Prof. Hecken