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
Mirdametinib (neurofibromatosis type 1 (NF1); ≥ 2 years)

From 19 March 2026

At their session on 19 March 2026, 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. In Annex XII, information on the active ingredient Mirdametinib shall be added in alphabetical order as follows:

Mirdametinib

Resolution of: 19 March 2026
Entry into force on: 19 March 2026
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 17 July 2025):

Ezmekly as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above.

Therapeutic indication of the resolution (resolution of 19 March 2026):

See therapeutic indication according to marketing authorisation.

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

Mirdametinib 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 determine 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).

<u>Adults and children aged 2 years and above with symptomatic, inoperable plexiform neurofibromas (PN) in neurofibromatosis type 1 (NF1)</u>

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

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

Study results according to endpoints:[1]

Adults and children aged 2 years and above with symptomatic, inoperable plexiform neurofibromas (PN) in neurofibromatosis type 1 (NF1)

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	The data are not assessable.
Morbidity	↑	Advantage in the endpoint "change in tumour volume" (compared to baseline).
Health-related quality of life	n.a.	The data are not assessable.
Side effects	n.a.	The data are not assessable.
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		

ReNeu study

- Single-arm, multicentre phase IIb study
- Cohort 1 (children > 2 years and adolescents) and Cohort 2 (adults > 18 years)
- Primary treatment phase: 24 cycles (each consisting of 3-week treatment + 1-week break) = 96 weeks
- Long-term treatment phase (optional): Further cycles until the discontinuation criterion is met or mirdametinib becomes commercially available
- Data cut-off: 12.06.2024

[1] Data from the dossier assessment by the G-BA (published on 2 January 2026), unless otherwise indicated.

Mortality

The data are not assessable.

Morbidity

Endpoint	Mirdametinib		
	Children and adolescents (N = 56)	Adults (N = 58)	Total population (N = 114)
Change in tumour volume[a]			
Tumour volume at baseline [ml][b]			
n (%)	56 (100)	58 (100)	114 (100)
MV (SD)	255.0 (559.1)	450.0 (744.0)	354.2 (664.1)
Median (min; max)	98.9 (5; 3,630)	196.3 (1; 3,457)	128.2 (1; 3,360)
Best reduction in tumour volume achieved [%][c]			
n (%)	54 (96.4)	50 (86.2)	104 (91.2)
MV (SD)	-37.7 (32.7)	-40.6 (28.3)	-39.1 (30.5)
Median (min; max)	-42.6 (-98.1; 47.6)	-41.3 (-89.7; 12.8)	-41.9 (-98.1; 47.6)
6MWT (metres)[d] (presented additionally)			
Baseline			
n (%)	11 (100)	16 (100)	27 (100)
MV (SD)	417.4 (124.4)	410.1 (94.6)	413.0 (105.5)
Median (min; max)	428.0 (111; 588)	434.0 (197; 526)	433.0 (111; 588)
Cycle 9			
n (%)	8 (72.7)	11 (68.8)	19 (70.4)
MV (SD)	442.3 (88.4)	423.9 (72.5)	431.6 (77.8)
Median (min; max)	464.0 (291; 527)	428.0 (277; 580)	428.0 (277; 580)
Change at cycle 9			
n (%)	8 (72.7)	11 (68.8)	19 (70.4)
MV (SD)	1.9 (75.2)[e]	-6.5 (57.1)[e]	-3 (63.5)[e]
Median (min; max)	-2.5 (-100; 119)[e]	0 (-91; 74)[e]	0 (-100; 119)[e]
Objective response rate (ORR)[f] (presented additionally)			
Predefined (cycle 24)			

Available data[j]	54 (96.4)	50 (86.2)	104 (91.2)
Percentage of subjects with ORR	29 (51.8)	24 (41.4)	53 (46.5)
Percentage of subjects with confirmed CR[g]	0 (0)	0 (0)	0 (0)
Percentage of subjects with confirmed PR[h]	29 (51.8)	24 (41.4)	53 (46.5)
Post hoc (including the long-term treatment phase)			
Available data[j]	54 (96.4)	50 (86.2)	104 (91.2)
Percentage of subjects with ORR	31 (55.4)	27 (46.6)	58 (50.9)
Percentage of subjects with confirmed CR[g]	0 (0)	0 (0)	0 (0)
Percentage of subjects with confirmed PR[h]	31 (55.4)	27 (46.6)	58 (50.9)
Progression-free survival (PFS)[i] (presented additionally)			
Median progression-free survival (months) [95% CI]	n.a. [n.a.; n.a.]	n.a. [n.a.; n.a.]	n.a. [n.a.; n.a.]
Percentage of subjects with PFS	11 (19.6)	7 (12.1)	18 (15.8)
Censored data	45 (80.4)	51 (87.9)	96 (84.2)

Quality of life

Endpoint	**Mirdametinib**		
	Children and adolescents ≥ 5 years (N = 50)[l]	**Adults (N = 58)**	**Total population ≥ 5 years (N = 108)**
PedsQL – Improvement by ≥ 15%			
Total score	8 (16.0)	-[m]	-[m]
Physical functioning	10 (20.0)	-[m]	-[m]
Emotional functioning	14 (28.0)	-[m]	-[m]
Social functioning	10 (20.0)	-[m]	-[m]
School functioning	11 (22.0)	-[m]	-[m]

Side effects

Endpoint MedDRA system organ classes/ AEs of special interest	**Active ingredient**		
	Children and adolescents (N = 56)	**Adults (N = 58)**	**Total population (N = 114)**
Total adverse events (presented additionally)	56 (100)	58 (100)	114 (100)
Serious adverse events (SAEs)	11 (19.6)	11 (19.0)	22 (19.3)
Severe adverse events (CTCAE grade 3 or 4)	23 (41.1)	22 (37.9)	45 (39.5)
Therapy discontinuation due to adverse events	5 (8.9)	15 (25.9)	20 (17.5)
Severe adverse events according to MedDRA system organ class (with an incidence ≥ 10%)			
Investigations	11 (19.6)	-[k]	15 (13.2)
Skin and subcutaneous tissue disorders	-[k]	8 (13.8)	-[k]
AEs of special interest (with an incidence ≥ 10%)			
Investigations (CTCAE grade ≥ 2)	15 (26.8)	9 (15.5)	24 (21.1)
Sputum fraction reduced	15 (26.8)	9 (15.5)	24 (21.1)
Skin and subcutaneous tissue disorders (CTCAE grade ≥ 3)	-[k]	6 (10.3)	-[k]

a. The evaluation was carried out using 3D MRI volumetric determination.
b. The baseline is defined as the last data collection prior to the start of treatment (in this case, the screening value).
c. Subjects without post-baseline values were treated as missing.
d. The difference was calculated only for the 19 participants who were surveyed at both baseline and cycle 9.
e. The difference was calculated only for participants who were surveyed at both baseline and cycle 9.
f. Primary endpoint of the ReNeu study. A confirmed objective response is defined as 2 consecutive assessments of PR or CR by the BICR within a period of 2 to 6 months.
g. Complete tumour regression.
h. A reduction in tumour volume by ≥ 20% compared to baseline.
i. The time, in months, from the start of treatment to the MRI examination at which disease progression (an increase in tumour volume by ≥ 20% compared to baseline) was observed.
j. Patients with post-baseline MRI measurement
k. The event occurred in < 10% of the subjects.
l. The PedsQL was surveyed only for a sub-population of children and adolescents ≥ 5 years. Return rate at cycle 13: n = 36 (72.0%).
m. The return rate to the predefined primary evaluation time point (cycle 13) was below 70%.

Abbreviations used:
6MWT = 6-minute walk test; AD = absolute difference; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; FAS = full analysis set; HR = hazard ratio; CI = confidence interval; MRI = magnetic resonance imaging; MV = mean value; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; ORR = objective response rate; PR = partial response; SD = standard deviation; vs = versus

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

Adults and children aged 2 years and above with symptomatic, inoperable plexiform neurofibromas (PN) in neurofibromatosis type 1 (NF1)

Approx. 515 – 920 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 Ezmekly (active ingredient: mirdametinib) at the following publicly accessible link (last access: 10 March 2026):

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

Treatment with mirdametinib should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with NF1-related tumours, or specialists in paediatrics and adolescent medicine specialising in neuropaediatrics, paediatric haematology and oncology.

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency (EMA) will assess new information on this medicinal product at least annually and update the product information where necessary.

4. Treatment costs

Annual treatment costs:

Adults and children aged 2 years and above with symptomatic, inoperable plexiform neurofibromas (PN) in neurofibromatosis type 1 (NF1)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Mirdametinib	€ 79,031.49 – € 315,399.50[2]

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 15 January 2026)

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 aged 2 years and above with symptomatic, inoperable plexiform neurofibromas (PN) in neurofibromatosis type 1 (NF1)

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient approved in monotherapy.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between statutory 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.

[2] The lowest annual treatment costs result for the dose in the dosage form of tablets for oral suspension (TOS) in 2-year-olds. The highest annual treatment costs result for the dose in solid dosage form (hard capsules) in adults.

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 Ezmekly 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 not conducted to a relevant percentage within the scope of SGB V.

II. The resolution will enter into force on the day of its publication on the G-BA website on 19 March 2026.

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

Berlin, 19 March 2026

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken