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)

Selumetinib (reassessment after the deadline: neurofibromatosis (≥ 3 to < 18 years, type 1))

of 21 December 2023

At its session on 21 December 2023, 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 is amended as follows:

1. **The information on Selumetinib in the version of the resolution of 3 February 2022 (BAnz AT 04.04.2022 B2) is repealed.**
2. **Annex XII shall be amended in alphabetical order to include the active ingredient selumetinib as follows:**

Selumetinib

Resolution of: 21 December 2023
Entry into force on: 21 December 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 17 June 2021):

Koselugo as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above.

Therapeutic indication of the resolution (resolution of 21 December 2023):

See therapeutic indication according to marketing authorisation.

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

Selumetinib is approved as a medicinal product for the treatment of rare diseases under 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).

<u>Paediatric patients aged 3 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 selumetinib:

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

Study results according to endpoints:[1]

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	No data available in comparison with the control group.
Morbidity	↑	No data available in comparison with the control group. Advantage in the endpoint "change in tumour volume".
Health-related quality of life	n.a.	No data available in comparison with the control group.
Side effects	n.a.	No data available in comparison with the control group.
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		

SPRINT study: ongoing, open-label, single-arm phase I/II study

data cut-off: 31 March 2021

Mortality

No deaths occurred in the study.

Morbidity

Endpoint	Selumetinib	
	N	Patients with event n (%)
Objective response rate (presented additionally)		
NCI POB	50	34 (68)
ICR	50	No data available
Progression-free survival (PFS) (presented additionally)[a]		
NCI POB	50	10 (20)
ICR	50	No data available

[1] Data from the dossier assessment of the G-BA (published on 2. Oktober 2023), unless otherwise indicated.

Endpoint	Selumetinib	
	N	Patients with event n (%); MV (SD)
Change in tumour volume (best percentage volume reduction achieved)		
Baseline	50	50; 837.1 (925.01)
NCI POB	50	48; -26.5 (13.56)
ICR	50	No data available

Endpoint	Selumetinib	
	N[b]	Patients with event n (%)
Global assessment of clinical change by GIC, age 8 - 18 years, before cycle 13 [c]		
Tumour pain	29	15 (44.1)
Total pain	29	12 (35.3)
Tumour-associated morbidity	29	17 (50.0)

Endpoint	Selumetinib	
	N[b]	n (%)
Global assessment of clinical change by GIC, age 5 - 7 years, before cycle 25[c]		
Tumour pain	13	8 (57.1)
Total pain	13	6 (42.9)
Tumour-associated morbidity	13	9 (64.3)

Endpoint	Selumetinib	
	N[a]	Patients with event n (%)[d]
Worst patient-reported pain imaginable PN (NRS-11)[e]		
Baseline MV (SD)	33	 3.4 (3.2)
Before cycle 13 Improvement by ≥ 2 points[f] Deterioration by ≥ 2 points[g]	29	 17 (50.0) 0 (0)

Endpoint	N[b]	Selumetinib		
		Time [seconds] Median (min; max)	Z-score for time[h] Median (min; max)	Dropped pegs Median (min; max)
Grooved Pegboard Test (presented additionally)				
All participants - dominant hand				
Baseline	25	86.1 (41.0; 164.7)	1.1 (-1.0; 12.4)	1 (0; 6)
Before cycle 13	22	-2.46 (-61.3; 202.4)	-0.35 (-12.2; 19.5)	0 (-3; 6)
All participants - non-dominant hand, N = 25				
Baseline	24	100.1 (46.0; 505.9)	2.2 (-0.9; 39.2)	1 (0; 18)
Before cycle 13	21	-11.7 (-121.9; 134.8)	-0.62 (-11.0; 10.1)	0 (-16; 5)
Participants with unilateral PN – impaired hand; N = 17				
Baseline	16	88.8 (41.0; 505.9)	1.46 (-0.9; 39.2)	1.5 (0; 18)
Before cycle 13	15	-2.7 (-121.9; 70.4)	-0.50 (-11.0; 0.6)	-1 (-16; 2)
Participants with unilateral PN – unimpaired hand; N = 17				
Baseline	17	92.5 (41.0; 300.0)	1.78 (-1.0; 12.4)	1 (0; 8)
Before cycle 13	16	-3.6 (-111.0; 202.4)	-0.47 (-12.2; 19.5)	0 (-3; 6)
Participants with bilateral PN – dominant hand; N = 8				
Baseline	8	88.9 (51.0; 137.0)	1.93 (-0.1; 6.8)	0 (0; 1)
Before cycle 13	6	-18.6 (-43.1; 84.0)	-1.28 (-4.1; 11.3)	0 (-1; 0)
Participants with bilateral PN – non-dominant hand; N = 8				
Baseline	8	94.2 (46.0; 209.8)	2.14 (-0.2; 6.2)	0 (0; 4)
Before cycle 13	6	5.67 (-12.9; 134.8)	0.92 (-1.2; 10.1)	1 (-1; 5)

Endpoint	Selumetinib N = 33			
	Baseline		Before cycle 13	
	N[b]	MV (SD)	N[b]	LSM [95% CI][j]; p value
PROMIS, age: 8 - 18 years, patient-reported				
"Mobility" scale	23	46.57 (6.54)	20	1.51 [-1.54; 4.57]; 0.327
"Upper extremities" scale	22	45.95 (12.91)	19	1.70 [-1.15; 4.54]; 0.238

Endpoint	Selumetinib N = 9			
	Baseline		Before cycle 13	
	N[b]	MV (SD)	N[b]	MV (SD)
PROMIS, age: 5 - 7 years, parent-reported				
"Mobility" scale	8	35.23 (12.90)	7	3.96 (4.02)
"Upper extremities" scale	8	36.15 (5.87)	7	1.67 (4.11)

Endpoint	Eye affected by PN HOTV (logMAR) N = 10		Eye not affected by PN HOTV (logMAR) N = 10	
	N	Patients with event n (%)[i]	N	Patients with event n (%)[i]
Visual acuity				
Baseline MV (SD) [logMAR]	5	0.54 (0.38)	7	0.01 (0.11)
Before cycle 37 Improvement by ≥ 0.2 logMAR Deterioration by ≥ 0.2 logMAR	4	 0 (0) 1 (20)	5	 0 (0) 0 (0)

Endpoint	Selumetinib	
	N[j]	Patients with event n (%) [95% CI]
Exophthalmos (presented additionally)[k]		
Right eye	7	2 (28.6) [3.7; 71.0]
Left eye	7	5 (71.4) [29.0; 96.3]
Eye impaired by PN	7	4 (57.1) [18.4; 90.1]
Eye not impaired by PN	7	3 (42.9) [9.9; 81.6]

Endpoint	Selumetinib	
	N[b]	Patients with event n (%)
Symptom checklist (presented additionally)[l,m]		
Tiredness/ fatigue Improvement on visit before cycle 25 Deterioration on visit before cycle 25	35	 14 (28.0) 8 (16.0)
Sleep disorders Improvement on visit before cycle 25 Deterioration on visit before cycle 25	35	 17 (34.0) 2 (4.0)
Reduced appetite Improvement on visit before cycle 25 Deterioration on visit before cycle 25	35	 9 (18.0) 4 (8.0)
Difficulty swallowing Improvement on visit before cycle 25 Deterioration on visit before cycle 25	35	 4 (18.0) 0 (0.0)
Snoring Improvement on visit before cycle 25 Deterioration on visit before cycle 25	35	 13 (26.0) 3 (6.0)
Waking up frequently at night Improvement on visit before cycle 25 Deterioration on visit before cycle 25	35	 16 (32.0) 3 (6.0)

Endpoint	Selumetinib	
	N[b]	Patients with event n (%)
Cough Improvement on visit before cycle 25 Deterioration on visit before cycle 25	35	 12 (24.0) 7 (14.0)
Nausea Improvement on visit before cycle 25 Deterioration on visit before cycle 25	35	 2 (4.0) 7 (14.0)
Weakness Improvement on visit before cycle 25 Deterioration on visit before cycle 25	35	 11 (22.0) 1 (2.0)
Muscle pain Improvement on visit before cycle 25 Deterioration on visit before cycle 25	35	 12 (24.0) 1 (2.0)

Health-related quality of life

Endpoint	Selumetinib	
	N[b]	Effect estimator
Changes in PedsQL total value, age 8 - 18 years, N = 34		
Baseline MV (SD)	33	73.9 (20.7)
Improvement by ≥ 15 points, before cycle 13 (n (%))[n]	29	7 (24.1)
Changes in PedsQL total value, age 3 - 7 years; N = 16		
Baseline	16	61.0 (18.2)
Improvement by ≥ 15 points, before cycle 25 (n (%))[n]	13	6 (37.5)

Side effects

Endpoint	Selumetinib	
	N	Patients with event n (%)
Total adverse events (presented additionally)		
	50	49 (98)
Serious adverse events (SAE)		
	50	15 (30)
Severe adverse events (CTCAE grade ≥ 3)		
	50	34 (68)
Therapy discontinuation due to adverse events[o]		
	50	6 (12)
SAE with an incidence ≥ 5%		
Infections and infestations	50	6 (12)
Gastrointestinal disorders	50	4 (8)

Endpoint	Selumetinib	
	N	Patients with event n (%)
Injury, poisoning and procedural complications	50	3 (6)
AE CTCAE grade 3 or higher with incidence ≥ 5% **SOC** PT		
Gastrointestinal disorders	50	**13 (26)**
Diarrhoea	50	8 (16)
Vomiting	50	4 (8)
Investigations	50	**12 (24)**
Elevated creatine phosphokinase level in the blood[1)]	50	3 (6)
Weight increased	50	4 (8)
Infections and infestations	50	**10 (20)**
Paronchia[1)]	50	4 (8)
Skin and subcutaneous tissue disorders	50	**6 (12)**
Acneiform dermatitis	50	3 (6)
Respiratory, thoracic and mediastinal disorders	50	**4 (8)**
Hypoxia	50	4 (8)
General disorders and administration site conditions	50	**4 (8)**
Pyrexia	50	4 (8)
Nervous system disorders	50	**4 (8)**

Endpoint	Selumetinib	
	N	Patients with event n (%)
Adverse Events of Special Interest (AESI) Preferred terms		
Heart failure	50	21 (42)
Decreased ejection fraction	50	13 (26)
Peripheral oedema	50	9 (18)
Peripheral swelling	50	1 (2)
Right ventricular ejection fraction reduced	50	1 (2)
Effects of erythropenia	50	27 (54)
Anaemia	50	27 (54)
Effects of leukopenia	50	29 (58)
Lymphocytopenia	50	15 (30)

Endpoint	Selumetinib	
	N	Patients with event n (%)
Neutropenia	50	19 (38)
Leukopenia	50	11 (22)
Muscle-related effects	50	44 (88)
Acute kidney injury	50	1 (2)
Elevated creatine phosphokinase level in the blood	50	39 (78)
Creatinine increased	50	17 (34)
Hypocalcaemia	50	15 (30)
Muscular weakness	50	1 (2)
Musculoskeletal pain	50	2 (4)
Myalgia	50	2 (2)
Diseases of the nail	50	28 (56)
Paronychia	50	28 (56)
Effects of oral mucositis	50	28 (56)
Cheilitis	50	2 (4)
Ulceration in the mouth	50	1 (2)
Stomatitis	50	26 (52)
Epiphyseal dysplasia	50	0 (0)
Rash, acneiform	50	28 (56)
Acneiform dermatitis	50	28 (56)
Rash, non-acneiform	50	38 (76)
Pruritus	50	26 (52)
Rash	50	3 (6)
Erythematous rash	50	1 (2)
Rash, maculopapular	50	25 (50)
Itchy rash	50	1 (2)
Ocular toxicities	50	10 (20)
Chorioretinal scar	50	1 (2)
Photophobia	50	2 (4)
Retinal detachment	50	1 (2)
Blurred vision	50	7 (14)
Visual field loss	50	1 (2)
Disorders of the vitreous body	50	1 (2)

Endpoint	Selumetinib	
	N	Patients with event n (%)
Effects of thrombocytopenia	50	6 (12)
Thrombocytopenia	50	6 (12)

[a] Progression according to REiNS criteria.
[b] Number of subjects with available data.
[c] Improvement defined as achieving the response categories "very much better" or "much better".
[d] Percentage based on all subjects who responded.
[e] Scale range from 0 "no pain" to 10 for "worst pain imaginable".
[f] At baseline, 11 study participants (33.3%) had a score < 2 and therefore, could not improve by 2 points.
[g] At baseline, 4 study participants (12.1%) had a score > 8 and, therefore, could not deteriorate by 2 points.
[h] Age (and gender)-standardised z-score.
[i] Percentage of subjects in relation to the FAS sub-population "subjects with an orbital PN" and available data at baseline.
[j] Patients with PN of the eye socket
[k] Data from the selumetinib module 4A dossier.
[l] Presentation of the results up to the survey period before cycle 25, as the return rate before cycle 37 is below 70%.
[m] Change defined as improvement or deterioration by one response category.
[n] Presentation of the results up to the survey period before cycle 13 or 25, as the return rate was below 70% thereafter. In addition to the responder analyses for an improvement by ≥15 points for the dossier (Module 4), post-hoc responder analyses for a deterioration by ≥ 15 points were submitted.
[O] Study participants received the study medication until the occurrence of disease progression, unacceptable AEs, withdrawal of consent, or decision of the medical investigator, whichever occurred earlier.

Abbreviations used:
CTCAE = Common Terminology Criteria for Adverse Events; GIC = Global Impression of Change; ICR = Independent Centralised Review; n.d. = no data available; CI = confidence interval; logMAR = Logarithm of the Minimum Angle of Resolution; LSM = Least Square Mean; MV = mean value; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; NCI POB = Paediatric Oncology Branch of the National Cancer Institute; PedsQL = Pediatric Quality of Life Inventory; PN = plexiform neurofibroma; PROMIS = Patient-Reported Outcomes Measurement Information System; SD = standard deviation; SOC = system organ class

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

Paediatric patients aged 3 years and above with symptomatic, inoperable plexiform neurofibromas (PN) in neurofibromatosis type 1 (NF1)

Approx. 510 to 740 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 Koselugo (active ingredient: selumetinib) at the following publicly accessible link (last access: 21 August 2023):

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

Treatment with selumetinib 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 will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Selumetinib	€ 96,064.35 - € 288,039.39

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 December 2023

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:

<u>Paediatric patients aged 3 years and above with symptomatic, inoperable plexiform neurofibromas (PN) in neurofibromatosis type 1 (NF1)</u>

- 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 authorised in monotherapy.

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 21 December 2023.**

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

Berlin, 21 December 2023

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

Prof. Hecken