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 Fedratinib (reassessment after the deadline: myelofibrosis)

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. In Annex XII, the information on the benefit assessment of Fedratinib in the version of the resolution of 2 September 2021 (BAnz AT 22.10.2021 B4) shall be amended as follows:

1. After the information:

   "Resolution of: 2 September 2021
   Entry into force on: 2 September 2021
   BAnz AT 22.10.2021 B4", the following information is inserted:

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

2. In the heading "Therapeutic indication of the resolution (resolution of 2 September 2021): see new therapeutic indication according to the marketing authorisation.", the information "resolution" is replaced by "resolutions" and the information "and of 21 August 2025" is inserted after the information "2 September 2021".

3. Number 1 "Extent of the additional benefit and significance of the evidence" shall be amended as follows:

   a) The information before the heading "Study results by endpoint" shall be amended as follows:

      a. In the heading at b), the information "patients" is deleted after the information "adults".

      b. Under the heading at b), after the information "Extent of the additional benefit and significance of the evidence of fedratinib", the information "Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification" is replaced by the following information:

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

   b) The information under the heading “Study results by endpoint:" shall be amended as follows:

      a. In the heading at b), the information "patients" is deleted after the information "adults".

      b. The information under the heading at b) is replaced by the following information:

"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 differences for the benefit assessment.
Health-related quality of life	n.a.	The data are not assessable.
Side effects	↓↓	Disadvantage in severe AEs (CTCAE grade ≥ 3). In detail, disadvantages in AEs of special interest.

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

FREEDOM2 study

- Open-label, multicentre RCT, phase III study, data cut-off from 27 December 2022
- Comparator study phase until the end of cycle 6 (24-week treatment phase)
- Fedratinib vs BAT (Best Available Therapy; predominantly ruxolitinib, transfusions with red blood cells and hydroxyurea), N=201, ratio 2:1
- Population: patients pretreated with ruxolitinib

Mortality

Endpoint	Fedratinib		BAT		Fedratinib vs BAT
	N	Patients with event n (%)	N	Patients with event n (%)	RR [b] [95% CI] p value[c]
Overall survival					
Death, until the end of cycle 6[a]	134	13 (9.70%)	67	3 (4.47%)	2.24 [0.66; 7.53] 0.19

Morbidity

Endpoint	Fedratinib		BAT		Fedratinib vs BAT
	N	Patients with event n (%)	N	Patients with event n (%)	RR [b] [95% CI] p value[c]
Spleen response ≥ 35% according to MRI/CT until the end of cycle 6 presented additionally [d]					
	134	48 (35.8%)	67	4 (5.97)	5.86 [2.21; 15.52] 0.0004

Endpoint	Fedratinib			BAT			Fedratinib vs BAT
	N	BL MV (SD)	Change cycle 6 MV (SE)	N	BL MV (SD)	Change cycle 6 MV (SE)	LS mean [95% CI][g] p value Hedges' g [95% CI][h]
Symptom response using MFSAF 4.0[e]							
	120[f]	29.3 (15.9)	16.6 (13.7)	65[f]	31.1 (17.3)	20.9 (13.3)	-5.1 [-8.97; -1.22]; no data available -0.39 [-0.70; -0.09]
EORTC QLQ-C30 (symptomatology)[i]							
No assessable data available.							
EQ-5D VAS (health status)[i]							
No assessable data available.							

Health-related quality of life

Endpoint	Fedratinib		BAT		Fedratinib vs BAT
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
EORTC QLQ-C30[i]					
No assessable data available.					

Side effects

Endpoint MedDRA system organ classes/ preferred terms/ AEs of special interest	Fedratinib		BAT		Fedratinib vs BAT
	N	Patients with event n (%)	N	Patients with event n (%)	RR[b] [95% CI] p value[c]
Total adverse events (presented additionally)	134	132 (98.51)	67	65 (97.01)	-
Serious adverse events (SAE)	134	89 (66.4)	67	29 (43.3)	1.45 [0.90; 2.35] 0.13
Severe adverse events (CTCAE grade 3 or 4)	134	46 (34.3)	67	16 (23.9)	1.53 [1.14; 2.05] 0.005
Therapy discontinuation due to adverse events	134	13 (9.70)	67	4 (5.97)	1.58 [0.54; 4.62] 0.40
Severe adverse events according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)					
No suitable data available.					
SAEs according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)					
No suitable data available.					
Adverse events of special interest (with statistically significant difference between the treatment arms)					
Thrombocytopenia with CTCAE grade 3 or 4	134	27 (20.1%)	67	4 (6.0%)	3.48 [1.30; 9.28] 0.01
Thiamine levels below the normal range with or without signs or symptoms of Wernicke's encephalopathy	134	23 (17.2%)	67	2 (3.0%)	5.52 [1.35; 22.64] 0.02

Encephalopathy, including Wernicke's encephalopathy or suspected cases of Wernicke's encephalopathy, associated with thiamine levels below the normal range	134	18 (13.4%)	67	2 (3.0%)	4.54 [1.07; 19.17] 0.04

a. Period for recording deaths: randomisation until the end of cycle 6 (≥ 24 weeks).
b. Mantel-Haenszel method estimated RR, stratified (by IRT) according to spleen size on palpation, platelet count and refractory or relapsed to ruxolitinib treatment versus intolerance to ruxolitinib treatment.
c. CI and p value calculated using normal approximation.
d. Primary endpoint of FREEDOM2.
e. The MFSAF v4.0 consists of 7 items, which are rated on an 11-point numerical scale from 0 (not present) to 10 (worst perceivable). The MFSAF-TSS is then calculated as the sum of the individual scores of the 7 items and can assume a range of values between 0 and 70, with a higher MFSAF-TSS value indicating more severe symptomatology.
f. The evaluation was based on the ITT population, for which a baseline value of the TSS of the MFSAF v4.0 > 0 is present (N=183).
g. Estimated using MMRM based on the change from baseline, taking into account all surveys until the end of cycle 6. The treatment arm, the baseline value, the visit and the treatment arm-visit interaction were included as fixed effects. The visit was considered a categorical variable and defined as a repeated measurement. An unstructured covariance matrix was used to model the correlation between the repeated measurements.
h. Calculation by the medical consultation.
i. Not assessable due to low return rates (< 70%)

Abbreviations used:
AD = absolute difference; BL = baseline; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; IRT = Interactive Response Technology; n.d. = no data available; CI = confidence interval; LS = least squares; MFSAF = Myelofibrosis Symptom Assessment Form; MMRM = mixed model for repeated measures; 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; RR = relative risk; SD = standard deviation; SE = standard error; SAE = (serious) adverse event; TSS = total symptom score; vs = versus

"

4. Number 2. "Number of patients or demarcation of patient groups eligible for treatment" shall be amended as follows:

   a) In the heading at b), the information "patients" is deleted after the information "adults".

   b) Under the heading at b), the information "Approx. 630 – 1,690 patients" is replaced by the information "Approx. 640 to 1,710 patients".

5. Under Number 4. "Treatment costs", the information after the heading "Annual treatment costs:" shall be amended as follows:

   a) The information "and b) Treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or

post essential thrombocythaemia myelofibrosis who have been treated with ruxolitinib" is deleted.

b) According to the information "Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 2021, the following information is inserted:

"b) <u>adults with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who have been treated with Ruxolitinib, treatment of disease-related splenomegaly or symptoms</u>

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Fedratinib	€ 43,732.48
Additionally required SHI costs	*€ 143.64*

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 August 2025)"

6. After Number 4. "Treatment costs", the following Number 5. is inserted:

"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:

b) <u>adults with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who have been treated with Ruxolitinib, treatment of disease-related splenomegaly or symptoms</u>

– 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.

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