Fedratinib (reassessment after the deadline: myelofibrosis)

Resolution of: 02.09.2021
Entry into force on: 02.09.2021
BAnz AT 22 10 2021 B4

Resolution of: 21 August 2025
Entry into force on: 21 August 2025
Federal Gazette, BAnz AT 25.09.2025 B3

Valid until: unlimited

Therapeutic indication (according to the marketing authorisation of 8 February 2021):

Inrebic is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve or have been treated with ruxolitinib.

Therapeutic indication of the resolution (resolutions of 2 September 2021 and of 21 August 2025):

see therapeutic indication according to marketing authorisation.

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

Fedratinib 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 German Social Code, Book Five (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).

(a) adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve, treatment of disease-related splenomegaly or symptoms

Extend of the additional benefit and significance of the evidence of fedratinib:

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

(b) 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

Extend of the additional benefit and significance of the evidence of fedratinib:

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

Study results according to endpoints:[1]

(a) adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve, treatment of disease-related splenomegaly or symptoms

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	no statistically significant or relevant difference
Morbidity	↑	Advantage in spleen response and symptom response
Health-related quality of life	∅	There are no usable data for the benefit assessment.
Side effects	↓ ↓	Disadvantage in severe AE CTCAE grade ≥ 3, advantage and disadvantage in AE 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
∅: there are no usable data for the benefit assessment.
n.a.: not assessable

[1] Data from the dossier assessment of the G-BA (published on 15. Juni 2021), and from the amendment to the dossier assessment from 13 August 2021 unless otherwise indicated.

JAKARTA study: RCT; fedratinib vs placebo, patients not pre-treated with JAK inhibitor

Mortality

Endpoint	**Fedratinib 400 mg**		**placebo**		Fedratinib vs placebo
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95 % CI] p-value
Overall survival					
Safety population - additional analyses[a] (at the end of treatment cycle 6)	96	*7 (7.3 %)*	95	*12 (12.6 %)*	0.58 [0.24; 1.40] 0.2188

Morbidity

	N	*Patients with event n (%) without event n (%) with imputed values (non responder) n (%)*	N	*Patients with event n (%) without event n (%) with imputed values (non responder) n (%)*	RR [95 % CI] p-value
Spleen response by MRI / CT (≥ 35%) at the end of treatment cycle 6					
with reconfirmation of a spleen response rate ≥ 35% 4 weeks later					
	96	*35 (36.5)* *40 (41.7)* *21 (21.9)*	96	*1 (1.0)* *57 (59.4)* *38 (39.6)*	35.00 [4.89; 250.36] < 0.0001
without reconfirmation of a spleen response rate ≥ 35% 4 weeks later					
	96	*45 (46.9)* *30 (31.3)* *21 (21.9)*	96	*1 (1.0)* *57 (59.4)* *38 (39.6)*	45.00 [6.33; 319.89] < 0.0001
	~~N~~	*Patients with event n (%)* [95 % CI]	N	*Patients with event n (%)* [95 % CI]	RR [95 % CI] p-value
Symptom response using modified MFSAF					
Symptom response rate (≥ 50% reduction in TSS) at the end of cycle 6[b]					
	89	36 (40.4) [30.2; 51.4]	81	7 (8.6) [30.2; 51.4]	4.68 [2.21; 9.92] < 0.0001
	N	Median time to event in weeks [95 % CI]	N	Median time to event in weeks [95 % CI]	HR [95 % CI] p-value

		Patients with event n (%)		*Patients with event n (%)*	
Symptom response using modified MFSAF[c]					
Time to improvement of ≥ 50 % compared to baseline					
Total symptom score (TSS)[d]	91	11.9 [8.0; 20.0] *56 (61.5)*	85	n.c. *22 (25.9)*	2.760 [1.678; 4.538] 0.0001
Night sweats	91	4.1 [4.0; 7.6] *60 (65.9)*	85	12.6 [8.0; n.c.] *30 (35.3)*	2.225 [1.428; 3.468] 0.0004
Itching	91	8.0 [7.9; 20.0] *44 (48.4)*	85	n.c. [12.0; n.c.] *20 (23.5)*	1.797 [1.058; 3.052] 0.0301
Abdominal disorders	91	8.1 [8.0; 16.1] *52 (57.1)*	85	n.c. [18.0; n.c.] *25 (29.4)*	1.980 [1.227; 3.195] 0.0051
Fullness	91	11.9 [8.0; 12.3] *53 (58.2)*	85	n.c. [12.0; n.c.] *24 (28.2)*	2.240 [1.377; 3.645] 0.0012
Pain under the ribs on the left side	91	8.0 [4.3; 12.0] *50 (54.9)*	85	24.0 [8.0; n.c.] *24 (28.2)*	1.854 [1.137; 3.023] 0.0133
Muscle / bone pain	91	24.0 [8.1; n.c.] *37 (40.7)*	85	n.c. *21 (24.7)*	1.682 [0.978; 2.893] 0.0602
Health status - EQ 5D-VAS[e]					
Time to improvement by ≥ 15 %[f]					
	91	26.4 [25.0; 26.4] *17 (18.7)*	88	24.9 [24.3; n.c.] *12 (13.6)*	0.866 [0.401; 1.870] 0.7148

Health-related quality of life

No data collected.

Side effects

Endpoint	**Fedratinib (400 mg)**		**placebo**		Fedratinib vs placebo
	N	Median in days [95 % CI] *Patients with event n (%)*	N	Median in days [95 % CI] *Patients with event n (%)*	HR [95 % CI] p-value
Adverse events in total					
	96	- *95 (99.0)*	95	- *89 (93.7)*	-
Serious adverse events (SAE)					
	96	n.c. *20 (20.8)*		n.c. *22 (23.2)*	0.84 [0.46; 1.54]; 0.5698
Severe adverse events (CTCAE grade ≥ 3)					
	96	115.0 [60.00; n.c.] *52 (54.2)*	95	n.c. [168.00; n.c.] *35 (36.8)*	1.67 [1.09; 2.57] 0.0178
Therapy discontinuation due to adverse events					
	96	n.c. *13 (13.5)*	95	n.c. *8 (8.4)*	1.41 [0.58; 3.42] 0.4511
Serious AEs with incidence ≥ 5% by system organ class and preferred term in either treatment group up to cycle 6 in the JAKARTA study; safety population **SOC** PT					
General disorders and administration site conditions	96	n.c. 5 (5.2)	95	n.c. 4 (4.2)	1.17 [0.31; 4.35] 0.8166
Blood and lymphatic system disorders	96	n.c. 33 (34.4)	95	n.c. 14 (14.7)	2.45 [1.31; 4.58] 0.0037
Anaemia	96	n.c. 29 (30.2)	95	n.c. 7 (7.4)	4.30 [1.88; 9.82] 0.0002
Thrombocytopenia	96	n.c. 5 (5.2)	95	n.c. 6 (6.3)	0.68 [0.20; 2.27] 0.5272
Gastrointestinal disorders	96	n.c. 8 (8.3)	95	n.c. 5 (5.3)	1.51 [0.49; 4.61] 0.4699
Diarrhoea	96	n.c. 5 (5.2)	95	n.c. 0 (0.0)	2,69E7 [0.00; n. c.] 0.0338
Heart diseases	96	n.c.	95	n.c.	1.40 [0.50; 3.92]

		9 (9.4)		6 (6.3)	0.5256
Cardiac insufficiency	96	n.c. 6 (6.3)	95	n.c. 2 (2.1)	2.76 [0.56; 13.71] 0.1945
Infections and infestations	96	n.c. 1 (1.0)	95	n.c. 6 (6.3)	0.14 [0.02; 1.20] 0.0369
Metabolic and nutritional disorders	96	n.c. 4 (4.2)	95	n.c. 5 (5.3)	0.75 [0.20; 2.81] 0.6722
Investigations	96	n.c. 7 (7.3)	95	n.c. 1 (1.1)	6.76 [0.83; 54.98] 0.0384
SAE with incidence ≥ 5% by system organ class and preferred term in either treatment group through cycle 6 in the JAKARTA study ; safety population					
Gastrointestinal disorders	96	n.c. 3 (3.1)	95	n.c. 5 (5.3)	0.52 [0.12; 2.17] 0.3586
Heart diseases	96	n.c. 9 (9.4)	95	n.c. 5 (5.3)	1.62 [0.54; 4.84] 0.3828
Cardiac insufficiency	96	n.c. 5 (5.2)	95	n.c. 3 (3.2)	1.54 [0.37; 6.45] 0.5521
Infections and infestations	96	n.c. 3 (3.1)	95	n.c. 5 (5.3)	0.54 [0.13; 2.25] 0.3876
AE of special interest up to cycle 6 in the JAKARTA study; safety population					
	N	Median in days / subjects with event	N	Median in days / subjects with event	HR [95 % CI] p-value
Time to onset of first potential Wernicke's encephalopathy					
Total Serious Severe (CTCAE grade ≥ 3)	96	n.c./10 (10.4) n.c./0 (0.0) n.c./1 (1.0)	95	4 (4.2) 0 (0.0) 0 (0.0)	2.39 [0.75; 7.63] 0.1288 n.c. 2,93E7 [0,00; n. c.] 0.3198
Time to first bleeding (SMQ bleeding, narrow definition)					
Total	96	n.c./0	95	n.c./0	n.c.
Time to first bleeding (SMQ bleeding, broad definition)					
Total Serious Severe (CTCAE grade ≥ 3)	96	n.c./1 (1.0) n.c./0 (0.0) n.c./1 (1.0)	95	n.c./0 (0) n.c./0 (0) n.c./0 (0)	2,9E7 [0,00; n. c.] 0.3224 n.c. 2,9E7 [0,00; n. c.] 0.3224
Time to onset of first cardiac insufficiency/cardiomyopathy					
Total	96	n.c./21 (21.9)	95	n.c./18 (18.9)	1.11 [0.59; 2.08] 0.7519

Serious Severe (CTCAE grade ≥ 3)		n.c./9 (9.4) n.c./8 (8.3)		n.c./8 (8.4) n.c./8 (8.4)	1.00 [0.38; 2.59] 0.9948 0.90 [0.34; 2.39] 0.8290
Time until the appearance of the first anaemia					
Total (CTCAE grade 3 or 4) Serious	96	n.c./30 (31.2) n.c./2 (2.1)	95	n.c./7 (7.4) n.c./1 (1.1)	4.48 [1.97; 10.21] < 0.0001 1.97 [0.18; 21.74] 0.5720
Time to first thrombocytopenia, CTCAE grade 3 or 4					
Total (CTCAE grade 3 or 4) Serious	96	n.c./1 (1.0) n.c./0 (0.0)	95	n.c./3 (3.2) n.c./3 (3.2)	0.31 [0.03; 2.98] 0.2831 0.00 [0.00; n. a.] 0.0679
Time to first elevation of ALT, AST or bilirubin in the blood					
Total (CTCAE grade 3 or 4) Serious	96	n.c./1 (1.0) n.c./0 (0.0)	95	n.c./3 (3.2) n.c./3 (3.2)	0.31 [0.03; 2.98] 0.2831 0.00 [0.00; n. a.] 0.0679
Time to first hyperamylasaemia or hyperlipasemia, CTCAE grade 3 or 4					
Total (grade 3 or 4) Serious	96	n.c./3 (3.1) n.c./1 (1.0)	95	n.c./1 (1.1) n.c./0 (0.0)	2.96 [0.31; 28.44] 0.3243 2,93E7 [0,00; n. c.] 0.3198
Time to first appearance of secondary malignancy					
Total Serious Severe (CTCAE grade ≥ 3)	96	n.c. / 0 (0) n.c. / 0 (0) n.c. / 0 (0)	95	n.c./ 5 (5.3) n.c./ 3 (3.2) n.c./ 3 (3.2)	0.00 [0.00; n. a.] 0.0154 0.00 [0.00; n. a.] 0.0611 0.00 [0.00; n. a.] 0.0514

[a] Due to the early study discontinuation and the associated short follow-up, no a priori defined analyses were performed according to the information provided by the pharmaceutical company.
[b] Symptom analysis population
[c] The evaluation was based on the ITT population using the Modified MFSAF HRQoL-evaluable population, defined as all patients in the ITT population for whom a baseline value was available (at least 5 of the 7 daily values in a week).
[d] The TSS is defined as the average of the daily total score of the six items of the MFSAF when at least 5 of the 7 daily scores were available in a week: Night sweats, itching, abdominal discomfort, early satiety, pain under the ribs on the left side, and bone or muscle pain.
[e] Evaluation was based on the ITT population using the EQ-5D-VAS HRQoL-evaluable population, defined as all subjects in the ITT population for whom a baseline value was available.
[f] Values between 0 (worst possible health status) and 100 (best possible health status).

Abbreviations used: CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; CI = confidence interval; MFSAF = Myelofibrosis Symptom Assessment Form; N = number of patients evaluated; n = number of patients with (at least one) event; n. c. = not calculable; n. a. = not achieved; PT = preferred term; RR = relative risk; SOC = system organ class; TSS = total symptom score vs = versus

(b) 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

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

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

(a) adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve, treatment of disease-related splenomegaly or symptoms

approx. 740 to 3,590 patients

(b) 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

approx. 640 to 1,710 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 Inrebic (active ingredient: fedratinib) at the following publicly accessible link (last access: 29 July 2021):
https://www.ema.europa.eu/documents/product-information/inrebic-epar-product-information_de.pdf

Initiation and monitoring of treatment with fedratinib should be performed only by specialists in internal medicine and haematology and oncology experienced in the therapy of patients with myelofibrosis.

In view of the risk of occurrence of (Wernicke's) encephalopathies, patients' thiamine levels should be assessed prior to initiation and at regular intervals during treatment (e.g., monthly for the first 3 months and every 3 months thereafter) and as clinically indicated.

4. Treatment costs

Annual treatment costs:

(a) adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve, treatment of disease-related splenomegaly or symptoms

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Fedratinib	€ 65,005.77
Additionally required SHI services	€ 156.10

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 2021)

b) 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

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)

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) 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

- 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.