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) and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Enfortumab vedotin (new therapeutic indication: urothelial cancer, unresectable or metastatic, first-line, eligible for platinum-containing chemotherapy, combination with pembrolizumab)

of 3 April 2025

At their session on 3 April 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 following information shall be added after No. 5 to the information on the benefit assessment of Enfortumab vedotin in accordance with the resolution of 1 December 2022 last modified on 24 January 2023:

Enfortumab vedotin

Resolution of: 3 April 2025
Entry into force on: 3 April 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 26 August 2024):

Padcev, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy.

Therapeutic indication of the resolution (resolution of 3 April 2025):

See new therapeutic indication according to marketing authorisation.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

a) Adults with unresectable or metastatic urothelial carcinoma who are eligible for a cisplatin-based therapy; first-line treatment

Appropriate comparator therapy:

Cisplatin in combination with gemcitabine followed by avelumab as maintenance treatment (maintenance treatment with avelumab only for patients who are progression-free)

Extent and probability of the additional benefit of enfortumab vedotin in combination with pembrolizumab compared with cisplatin in combination with gemcitabine (if applicable followed by avelumab maintenance treatment):

Indication of non-quantifiable additional benefit.

b) Adults with unresectable or metastatic urothelial carcinoma who are not eligible for a cisplatin-based therapy; first-line treatment

Appropriate comparator therapy:

Carboplatin in combination with gemcitabine in accordance with Annex VI to Section K of the Pharmaceuticals Directive followed by avelumab as maintenance treatment (maintenance treatment with avelumab only for patients who are progression-free)

Extent and probability of the additional benefit of enfortumab vedotin in combination with pembrolizumab compared with carboplatin in combination with gemcitabine (if applicable followed by avelumab maintenance treatment):

Indication of a considerable additional benefit.

Study results according to endpoints:[1]

a) Adults with unresectable or metastatic urothelial carcinoma who are eligible for a cisplatin-based therapy; first-line treatment

Indication of non-quantifiable additional benefit

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	↑	Advantages in the symptom scales "nausea and vomiting", "constipation" and "appetite loss"
Health-related quality of life	↔	No relevant differences for the benefit assessment
Side effects	↑	Advantage for severe UEs; disadvantages and advantages for specific AEs in detail
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		

- EV-302 / KN-A39 study: Enfortumab vedotin + pembrolizumab **vs** cisplatin/ carboplatin + gemcitabine
- Relevant sub-population: Patients who are eligible for a cisplatin-based therapy (n = 282)
- Ongoing, multicentre, open-label, randomised phase III study
- 2nd data cut-off from 8 August 2024

[1] Data from the dossier assessment of the IQWiG (A24-98) and from the addendum (A25-22), unless otherwise indicated.

Mortality

Endpoint	**Enfortumab vedotin+ pembrolizumab**		**Cisplatin + gemcitabine (if applicable, followed by avelumab maintenance treatment)**		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[a] Absolute difference (AD)[b]
Mortality					
Overall survival	240	36.7 [31.5; n.c.] *100 (41.7)*	242	18.4 [16.4; 21.6] *149 (61.6)*	0.54 [0.42; 0.70] < 0.001 AD = + 18.1 months
Overall survival (sensitivity analysis 1[c])	240	36.7 [31.5; n.c.] *100 (41.7)*	242	26.5 [19.5; n.c.] *114 (47.1)*	0.71 [0.54; 0.93] 0.012 AD = + 10.2 months
Overall survival (sensitivity analysis 2[d])	240	36.7 [31.5; n.c.] *100 (41.7)*	242	28.6 [21.1; n.c] *114 (47.1)*	0.79 [0.60; 1.03] 0.077 AD = + 8.1 months
Overall survival (sensitivity analysis 3[e])	240	36.7 [31.5; n.c.] *100 (41.7)*	242	21.9 [19.5; 26.6] *140 (57.9)*	0.61 [0.47; 0.79] 0.0002 AD = + 14.8 months

Morbidity

Endpoint	Enfortumab vedotin+ pembrolizumab		Cisplatin + gemcitabine (if applicable, followed by avelumab maintenance treatment)		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[b]
Progression-free survival (PFS)[2]					
	240	15.0 [10.4; 20.4] *137 (57.1)*	242	6.5 [6.3; 8.1] *163 (67.4)*	0.51 [0.41; 0.65] < 0.0001 AD = + 8.5 months
Pain (BPI-SF – time to 1st deterioration[f])					
Worst pain (BPI-SF item 3)	240	2.0 [1.3; 4.5] *132 (55.0)*	242	1.8 [1.1; 3.2] *115 (47.5)*	0.89 [0.68; 1.17] 0.410
Pain intensity (BPI-SF items 3-6) (presented additionally)	*240*	*12.1 [7.3; 28.6]* *99 (41.3)*	*242*	*n.r. [8.1; n.c.]*	*1.04* *[0.75; 1.46]* *0.802*
Impairment due to pain (BPI-SF item 9a–9g)	240	2.3 [1.5; 5.2] *137 (57.1)*	242	2.0 [1.1; 4.5] *109 (45.0)*	0.95 [0.72; 1.26] 0.726
Symptomatology (EORTC QLQ-C30 – time to 1st deterioration[g])					
Fatigue	240	0.4 [0.4; 0.6] *170 (70.8)*	242	0.4 [0.4; 0.6] *158 (65.3)*	0.80 [0.63; 1.02] 0.080
Nausea and vomiting	240	2.0 [1.1; 4.6] *134 (55.8)*	242	0.4 [0.4; 0.8] *142 (58.7)*	0.56 [0.43; 0.73] < 0.001 AD = + 1.6 months
Pain	240	0.7 [0.5; 1.3] *151 (62.9)*	242	1.1 [0.6; 1.4] *130 (53.7)*	1.04 [0.80; 1.35] 0.793
Dyspnoea	240	2.4 [1.6; 4.6] *140 (58.3)*	242	2.0 [1.7; 3.9] *109 (45.0)*	1.04 [0.79; 1.37] 0.773
Insomnia	240	2.3 [0.9; 4.5] *127 (52.9)*	242	2.0 [0.9; 3.8] *116 (47.9)*	0.76 [0.58; 1.01]

[2] Data from the information subsequently submitted by the pharmaceutical company in the written statement procedure from 23 January 2025

Endpoint	**Enfortumab vedotin+ pembrolizumab**		**Cisplatin + gemcitabine (if applicable, followed by avelumab maintenance treatment)**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[b]
					0.063
Appetite loss	240	0.9 [0.6; 1.7] *144 (60.0)*	242	0.6 [0.4; 0.9] *132 (54.5)*	0.75 [0.58; 0.97] 0.024 AD = + 0.3 months
Constipation	240	2.2 [1.5; 4.5] *128 (53.3)*	242	0.7 [0.4; 1.3] *134 (55.4)*	0.59 [0.46; 0.78] < 0.001 AD = + 1.5 months
Diarrhoea	240	2.0 [1.3; 3.8] *139 (57.9)*	242	3.1 [2.0; 9.3] *98 (40.5)*	1.13 [0.86; 1.50] 0.371
Health status (EQ-5D VAS – time to 1st deterioration[h])					
	240	2.5 [1.3; 5.2] *144 (60.0)*	242	2.2 [1.5; 3.2] *113 (46.7)*	1.02 [0.78; 1.34] 0.913

Health-related quality of life

Endpoint	**Enfortumab vedotin+ pembrolizumab**		**Cisplatin + gemcitabine (if applicable, followed by avelumab maintenance treatment)**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[a] Absolute difference (AD)[b]
EORTC QLQ-C30 – time to 1st deterioration[i]					
Global health status	240	0.7 [0.6; 1.3] *158 (65.8)*	242	0.9 [0.6; 1.1] *133 (55.0)*	0.88 [0.68; 1.14] 0.344
Physical functioning	240	1.1 [0.6; 1.6] *165 (68.8)*	242	0.9 [0.6; 1.1] *138 (57.0)*	0.92 [0.72; 1.18] 0.472
Role functioning	240	0.6 [0.4; 0.8] *166 (69.23)*	242	0.4 [0.4; 0.9] *140 (57.9)*	0.90 [0.70; 1.16] 0.469
Emotional functioning	240	3.2 [2.0; 10.1] *126 (52.5)*	242	3.8 [2.0; 11.4] *96 (39.7)*	1.02 [0.76; 1.36] 0.905
Cognitive functioning	240	1.8 [1.1; 2.3] *148 (61.7)*	242	0.9 [0.6; 1.5] *130 (53.7)*	0.89 [0.66; 1.16] 0.247
Social functioning	240	0.7 [0.5; 1.1] *164 (68.3)*	242	0.9 [0.6; 1.1] *130 (53.7)*	1.17 [0.90; 1.49] 0.236

Side effects

Endpoint	Enfortumab vedotin+ pembrolizumab		Cisplatin + gemcitabine (if applicable, followed by avelumab maintenance treatment)		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[j] Absolute difference (AD)[b]
Adverse events in total					
	239	0.2 [0.2; 0.2] *239 (100.0)*	236	0.1 [0.1; 0.2] *234 (99.2)*	-
Serious adverse events (SAE)					
	239	18.0 [9.5; n.c.] *112 (46.9)*	236	n.r. *83 (35.2)*	0.91 [0.67; 1.23] 0.543
Severe adverse events (CTCAE grade 3 or 4)					
	239	4.2 [3.0; 6.0] *168 (70.3)*	236	1.4 [1.0; 1.8] *175 (74.2)*	0.52 [0.41; 0.66] < 0.001 AD = + 2.8 months
Therapy discontinuation due to adverse events					
	239	12.2 [9.7; 17.9] *110 (38.5)*	236	n.r. *58 (24.6)*	0.73 [0.50; 1.06] 0.095
Specific adverse events					
Immune-mediated AEs (presented additionally)	239	12.6 [7.2; n.c.] *108 (45.2)*	236	n.r. *10 (4.2)*	-
Immune-mediated SAEs	239	n.r. *36 (15.1)*	236	n.r. *2 (0.8)*	11.08 [2.61; 46.92] < 0.001
Immune-mediated severe AEs	239	n.r. *51 (21.3)*	236	n.r. *3 (1.3)*	11.07 [3.40; 36.11] < 0.001
Peripheral neuropathy (SMQ, AEs)	239	4.4 [3.5; 5.1] *163 (68.2)*	236	n.r. *43 (18.2)*	3.30 [2.33; 4.67] < 0.001
Skin reactions	239	0.5 [0.4; 0.6] *204 (85.4)*	236	n.r. *61 (25.8)*	5.90 [4.40; 7.89] < 0.001

Endpoint	**Enfortumab vedotin+ pembrolizumab**		**Cisplatin + gemcitabine (if applicable, followed by avelumab maintenance treatment)**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[j] Absolute difference (AD)[b]
Severe hyperglycaemia (PT, severe AEs)	239	n.r. *19 (7.9)*	236	n.r. *2 (0.8)*	7.70 [1.77; 33.57] 0.001
Severe nephrotoxicity	239	n.r. *17 (7.1)*	236	n.r. *16 (6.8)*	0.69 [0.33; 1.46] 0.330
Nausea (PT, AEs)	239	n.r. *63 (26.4)*	236	3.3 [2.1; n.c.] *120 (50.8)*	0.36 [0.26; 0.49] < 0.001
Vomiting (PT, AEs)	239	n.r. *27 (11.3)*	236	n.r. *42 (17.8)*	0.47 [0.28; 0.79] 0.004
Eye disorders (SOC, AEs)	239	24.6 [12.7; n.c.] *93 (38.9)*	236	n.r. *14 (5.9)*	5.30 [2.98; 9.41] < 0.001
Ear and labyrinth disorders (SOC, AEs)	239	n.r. *17 (7.1)*	236	n.r. *33 (14.0)*	0.17 [0.07; 0.40] < 0.001
Endocrine disorder (SOC, SAEs)	239	n.r. *40 (16.7)*	236	n.r. *2 (0.8)*	13.47 [3.21; 56.56] < 0.001
Gastrointestinal disorders (SOC, SAEs)	239	n.r. *28 (11.7)*	236	n.r. *6 (2.5)*	3.22 [1.29; 7.99] 0.008
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	239	n.r. *26 (10.9)*	236	n.r. *4 (1.7)*	4.07 [1.37; 12.04] 0.006
Blood and lymphatic system disorders (SOC, severe AEs)	239	n.r. *17 (7.1)*	236	4.9 [3.0; n.c.] *110 (46.6)*	0.08 [0.05; 0.15] < 0.001
Urinary tract infection (PT, severe AEs)	239	n.r. *8 (3.3)*	236	6.1 [6.1; n.c.] *19 (8.1)*	0.32 [0.13; 0.76] 0.007

Endpoint	Enfortumab vedotin+ pembrolizumab		Cisplatin + gemcitabine (if applicable, followed by avelumab maintenance treatment)		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[j] Absolute difference (AD)[b]
Diarrhoea (PT, severe AEs)	239	n.r. *11 (4.6)*	236	n.r. *2 (0.8)*	4.34 [0.94; 20.10] 0.040
General disorders and administration site conditions (SOC, severe AEs)	239	n.r. *17 (7.1)*	236	n.r. *24 (10.2)*	0.30 [0.14; 0.68] 0.002
Hepatobiliary disorders (SOC, severe AEs)	239	n.r. *11 (4.6)*	236	n.r. *1 (0.4)*	7.95 [0.995; 63.60] 0.020

[a] HR and CI: Cox proportional hazards model; p value: log-rank test, each stratified by PD-L1 expression (high vs low) and liver metastases (present vs absent)
[b] Data on absolute difference (AD) only in the case of statistically significant difference; own calculation
[c] Censoring at the time of death: Avelumab-eligible patients who did not receive avelumab and died were censored at the time of death.
[d] Censoring for the data cut-off: Avelumab-eligible patients who did not receive avelumab and died were censored at the time of the data cut-off
[e] Modified date of death: Avelumab-eligible patients who did not receive avelumab and died were imputed with a modified time of death. A simplified assumption was made that the patients would have benefited from therapy with avelumab to the same extent as was shown in the approval study of avelumab (JAVELIN Bladder 100)
[f] An increase in score by ≥ 2 points compared to the start of the study is considered a clinically relevant deterioration (scale range: 0 to 10)
[g] An increase in EORTC QLQ-C30 score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range: 0 to 100).
[h] A decrease in EQ-5D VAS score by ≥ 15 points compared to the start of study is considered clinically relevant deterioration (scale range: 0 to 100).
i A decrease in EORTC QLQ-C30 score by ≥ 10 points compared to the baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
[j] HR and CI: unstratified Cox proportional hazards model; p value: unstratified log-rank test

Abbreviations used:
AD = absolute difference; BPI-SF = Brief Pain Inventory – Short Form; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; PD-L1 = Programmed Cell Death-Ligand 1; PT = preferred term; SOC = system organ class; VAS = visual analogue scale; vs = versus

b) Adults with unresectable or metastatic urothelial carcinoma who are not eligible for a cisplatin-based therapy; first-line treatment

Indication of a considerable additional benefit.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	↑	Advantages for the endpoint "worst pain" and in the symptom scales "nausea and vomiting" and "constipation"
Health-related quality of life	↔	No relevant differences for the benefit assessment
Side effects	↑	Advantage for severe UEs; disadvantages and advantages for specific AEs in detail
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		

- EV-302 / KN-A39 study: Enfortumab vedotin + pembrolizumab **vs** cisplatin/ carboplatin + gemcitabine
- Relevant sub-population: Patients who are **not** eligible for a cisplatin-based therapy
- Ongoing, multicentre, open-label, randomised phase III study
- 2nd data cut-off from 8 August 2024

Mortality

Endpoint	**Enfortumab vedotin+ pembrolizumab**		**Carboplatin + gemcitabine (if applicable followed by avelumab maintenance treatment)**		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[a] Absolute difference (AD)[b]
Mortality					
Overall survival	202	25.6 [23.0; 36.3] 103 (51.0)	202	12.9 [11.3; 15.0] 148 (73.3)	0.47 [0.37; 0.63] < 0.0001 AD = + 12.7 months
Overall survival (sensitivity analysis 1[c])	202	25.6 [23.0; 36.3] 103 (51.0)	202	15.0 [12.2; 20.0] 148 (73.3)	0.61 [0.47; 0.80] 0.0002 AD = + 10.6 months
Overall survival (sensitivity analysis 2[d])	202	25.6 [23.0; 36.3] 103 (51.0)	202	15.9 [12.5; 21.2] 120 (59.4)	0.71 [0.55; 0.93] 0.0110[a] AD = + 9.7 months
Overall survival (sensitivity analysis 3[e])	202	25.6 [23.0; 36.3] 103 (51.0)	202	14.7 [12.5; 18.3] 143 (70.8)	0.54 [0.42; 0.70] < 0.001[a] AD = + 10.9 months

Morbidity

Endpoint	Enfortumab vedotin+ pembrolizumab		Carboplatin + gemcitabine (if applicable followed by avelumab maintenance treatment)		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[b]
Progression-free survival (PFS)[3]					
	202	10.6 [8.3; 14.6] 125 (61.9)	202	6.1 [5.8; 6.2] 154 (76.2)	0.45 [0.35; 0.57] < 0.0001 AD = + 4.5 months
Pain (BPI-SF – time to 1st deterioration[f])					
Worst pain (BPI-SF item 3)	202	3.2 [1.6; 13.5] 88 (43.6)	202	1.3 [0.7; 2.2] 107 (53.0)	0.67 [0.49; 0.92] 0.012
Pain intensity (BPI-SF items 3-6) (presented additionally)	202	19.7 [10.8; n.c.] 69 (34.2)	202	5.9 [2.4; 8.0] 86 (42.6)	0.61 [0.42; 0.88] 0.008
Impairment due to pain (BPI-SF item 9a–9g)	202	2.7 [1.3; 10.8] 90 (44.6)	202	1.3 [0.8; 2.0] 112 (55.4)	0.74 [0.54; 1.02] 0.069
Symptomatology (EORTC QLQ-C30 – time to 1st deterioration[g])					
Fatigue	202	0.6 [0.4; 0.8] 131 (64.9)	202	0.4 [0.4; 0.6] 132 (65.3)	0.77 [0.58; 1.02] 0.068
Nausea and vomiting	202	1.8 [1.1; 2.7] 105 (50.5)	202	1.1 [0.4; 1.5] 118 (58.4)	0.72 [0.54; 0.97] 0.037 AD = + 0.7 months
Pain	202	1.1 [0.7; 2.0] 110 (52.5)	202	0.9 [0.5; 1.3] 120 (59.4)	0.79 [0.59; 1.06] 0.110
Dyspnoea	202	2.0 [1.5; 3.1] 104 (51.5)	202	1.5 [1.1; 2.2] 108 (53.5)	0.85 [0.62; 1.15] 0.299
Insomnia	202	1.6 [1.1; 2.2] 102 (50.5)	202	1.3 [0.9; 2.2] 96 (47.5)	0.87 [0.64; 1.20] 0.409

[3] Data from Module 4 of the benefit assessment dossier from 20 September 2024

Endpoint	**Enfortumab vedotin+ pembrolizumab**		**Carboplatin + gemcitabine (if applicable followed by avelumab maintenance treatment)**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[b]
Appetite loss	202	0.9 [0.7; 1.3] 118 (58.4)	202	1.1 [0.6; 1.5] 110 (54.5)	0.96 [0.71; 1.30] 0.859
Constipation	202	2.2 [1.5; 3.1] 97 (48.0)	202	0.4 [0.4; 0.9] 113 (55.9)	0.49 [0.36; 0.68] < 0.0001 AD = + 1.8 months
Diarrhoea	202	2.0 [1.3; 3.1] 104 (51.5)	202	4.6 [2.0; 11.0] 79 (39.1)	1.33 [0.96; 1.85] 0.075
Health status (EQ-5D VAS – time to 1st deterioration[h])					
	202	1.5 [1.0; 3.2] 110 (54.5)	202	1.3 [0.9; 2.0] 111 (55.0)	0.89 [0.66; 1.21] 0.508

Health-related quality of life

Endpoint	**Enfortumab vedotin+ pembrolizumab**		**Carboplatin + gemcitabine (if applicable followed by avelumab maintenance treatment)**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[a] Absolute difference (AD)[b]
EORTC QLQ-C30 – time to 1st deterioration[i]					
Global health status	202	1.1 [0.6; 1.5] 123 (60.9)	202	0.9 [0.6; 1.1] 116 (57.4)	0.96 [0.71; 1.30] 0.841
Physical functioning	202	1.1 [0.7; 1.7] 126 (62.4)	202	0.7 [0.4; 1.1] 126 (62.4)	0.82 [0.61; 1.09] 0.168
Role functioning	202	0.7 [0.5; 1.1] 126 (62.4)	202	0.4 [0.4; 0.6] 137 (67.8)	0.76 [0.56; 1.01] 0.063
Emotional functioning	202	4.5 [2.5; 9.4] 92 (45.5)	202	2.0 [1.1; 3.2] 96 (47.5)	0.74 [0.53; 1.04] 0.087
Cognitive functioning	202	1.5 [1.1; 2.0] 114 (56.4)	202	0.9 [0.6; 1.5] 117 (57.9)	0.80 [0.59; 1.07] 0.140
Social functioning	202	0.9 [0.6; 1.3] 122 (60.4)	202	0.9 [0.4; 1.1] 114 (56.4)	1.04 [0.77; 1.41] 0.752

Side effects

Endpoint	Enfortumab vedotin+ pembrolizumab		Carboplatin + gemcitabine (if applicable followed by avelumab maintenance treatment)		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[j] Absolute difference (AD)[b]
Adverse events in total					
	201	0.3 [0.2; 0.3] *200 (99.5)*	197	0.2 [0.1; 0.2] *193 (98.0)*	-
Serious adverse events (SAE)					
	201	7.9 [5.3; 13.1] *122 (56.2)*	197	5.4 [4.2; n.c.] *86 (43.7)*	0.87 [0.64; 1.18] 0.365
Severe adverse events (CTCAE grade 3 or 4)					
	201	2.6 [2.0; 4.0] *163 (81.1)*	197	0.7 [0.5; 0.9] *166 (84.3)*	0.46 [0.36; 0.58] < 0.001 AD = + 1.9 months
Therapy discontinuation due to adverse events					
	201	11.5 [8.9; 15.0] *102 (50.7)*	197	n.r. *35 (17.8)*	1.35 [0.88; 2.06] 0.169
Specific adverse events					
Immune-mediated AEs (presented additionally)	*201*	*11.0 [6.9; 23.9]* *93 (46.3)*	*197*	*n.r.* *11 (5.6)*	-
Immune-mediated SAEs	201	n.r. *24 (11.9)*	197	n.r. *2 (1.0)*	6.93 [1.58; 30.31] 0.003
Immune-mediated severe AEs	201	n.r. *45 (22.4)*	197	n.r. *2 (1.0)*	15.92 [3.82; 66.38] < 0.001
Peripheral neuropathy (SMQ, AEs)	201	4.5 [3.7; 5.1] *133 (66.2)*	197	n.r. *17 (8.6)*	6.41 [3.83; 10.73] < 0.001
Skin reactions	201	0.6 [0.5; 0.7] *163 (81.1)*	197	n.r. *51 (25.9)*	4.95 [3.60; 6.81] < 0.001

Endpoint	Enfortumab vedotin+ pembrolizumab		Carboplatin + gemcitabine (if applicable followed by avelumab maintenance treatment)		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[j] Absolute difference (AD)[b]
Severe hyperglycaemia (PT, severe AEs)[m]	201	n.r. *12 (6.0)*	197	n.r. *1 (0.5)*	10.71 [1.38; 82.92] 0.005
Severe nephrotoxicity	201	n.r. *28 (13.9)*	197	n.r. *15 (7.6)*	1.12 [0.57; 2.23] 0.736
Constipation (PT, AEs)	201	n.r. *50 (24.9)*	197	n.r. *71 (36.0)*	0.45 [0.30; 0.66] < 0.001
Diarrhoea (PT, AEs)	201	23.9 [11.1; n.c.] *80 (39.8)*	197	n.r. *29 (14.7)*	2.30 [1.48; 3.56] < 0.001
Dysgeusia (PT, AEs)	201	n.r. *46 (22.9)*	197	n.r. *9 (4.6)*	4.83 [2.35; 9.92] < 0.001
Eye disorders (SOC, AEs)	201	27.9 [17.5; n.c.] *66 (32.8)*	197	n.r. *12 (6.1)*	3.85 [2.04; 7.26] < 0.001
Endocrine disorder (SOC, SAEs)	201	n.r. *39 (19.4)*	197	n.r. *4 (2.0)*	5.47 [1.90; 15.79] < 0.001
Blood and lymphatic system disorders (SOC, severe AEs)	201	n.r. *47 (23.4)*	197	1.3 [1.0; 1.6] *135 (68.5)*	0.14 [0.09; 0.20] < 0.001
Acute kidney injury (PT, severe AEs)	201	n.r. *16 (8.0)*	197	n.r. *4 (2.0)*	3.05 [0.99; 9.36] 0.041

[a] HR and CI: Cox proportional hazards model; p value: log-rank test, each stratified by PD-L1 expression (high vs low) and liver metastases (present vs absent)
[b] Data on absolute difference (AD) only in the case of statistically significant difference; own calculation
[c] Censoring at the time of death: Avelumab-eligible patients who did not receive avelumab and died were censored at the time of death.
[d] Censoring for the data cut-off: Avelumab-eligible patients who did not receive avelumab and died were censored at the time of the data cut-off
[e] Modified date of death: Avelumab-eligible patients who did not receive avelumab and died were imputed with a modified time of death. A simplified assumption was made that the patients

Endpoint	Enfortumab vedotin+ pembrolizumab		Carboplatin + gemcitabine (if applicable followed by avelumab maintenance treatment)		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[j] Absolute difference (AD)[b]

would have benefited from therapy with avelumab to the same extent as was shown in the approval study of avelumab (JAVELIN Bladder 100)

[f] An increase in score by ≥ 2 points compared to the start of the study is considered a clinically relevant deterioration (scale range: 0 to 10)

[g] An increase in EORTC QLQ-C30 score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range: 0 to 100).

[h] A decrease in EQ-5D VAS score by ≥ 15 points compared to the start of study is considered clinically relevant deterioration (scale range: 0 to 100).

i A decrease in EORTC QLQ-C30 score by ≥ 10 points compared to the baseline is considered a clinically relevant deterioration (scale range: 0 to 100).

[j] HR and CI: unstratified Cox proportional hazards model; p value: unstratified log-rank test

Abbreviations used:
AD = absolute difference; AEOSI = Adverse Events of Special Interest; BPI-SF = Brief Pain Inventory – Short Form; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; PD-L1 = Programmed Cell Death-Ligand 1; PT = preferred term; SOC = system organ class; VAS = visual analogue scale; vs = versus

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

a) Adults with unresectable or metastatic urothelial carcinoma who are eligible for a cisplatin-based therapy; first-line treatment

Approx. 510 to 1,260 patients

b) Adults with unresectable or metastatic urothelial carcinoma who are not eligible for a cisplatin-based therapy; first-line treatment

Approx. 410 to 1020 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 Padcev (active ingredient: enfortumab vedotin) at the following publicly accessible link (last access: 25 March 2025):

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

Treatment with enfortumab vedotin should only be initiated and monitored by specialists in internal medicine, haematology, and oncology and urology, and specialists participating in the Oncology Agreement experienced in the treatment of adults with urothelial carcinoma.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients as well as a patient card. The patient is requested to carry the patient card with him/her at all times. The training material for health professionals and the patient card contain, in particular, instructions on how to deal with the skin reactions including severe skin reactions that can potentially occur with enfortumab vedotin.

4. Treatment costs

Annual treatment costs:

The annual treatment costs shown refer to the first year of treatment.

a) Adults with unresectable or metastatic urothelial carcinoma who are eligible for a cisplatin-based therapy; first-line treatment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Enfortumab vedotin in combination with pembrolizumab	
Enfortumab vedotin	€ 91,404.29
Pembrolizumab	€ 90,059.96
Total	€ 181,464.25
Appropriate comparator therapy:	
Cisplatin in combination with gemcitabine followed by avelumab as maintenance treatment (maintenance treatment with avelumab only for patients who are progression-free)	
Cisplatin	€ 463.72 – € 695.58
Gemcitabine	€ 2,159.04 – € 3,238.56
Total	€ 2,622.76 – € 3,934.14
Maintenance treatment with avelumab	
Avelumab	€ 44,412.74 (after 6 cycles of induction therapy) – € 57,012.10 (after 4 cycles of induction therapy)
Cisplatin and gemcitabine including subsequent maintenance treatment with avelumab	
Total	€ 48,346.88 (after 6 cycles of induction therapy) – € 59,634.86 (after 4 cycles of induction therapy)

Designation of the therapy	Annual treatment costs/ patient
Additionally required SHI services	€ 105.70 – € 110.55

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 March 2025)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Enfortumab vedotin in combination with pembrolizumab					
Enfortumab vedotin	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	2	34.8	€ 3,480
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	17.4 (21-day) or 8.7 (42-day)	€ 1,740 (21-day) or € 870 (42-day)
Appropriate comparator therapy					
Cisplatin in combination with gemcitabine					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	4.0 – 6.0	€ 400 – € 600
Gemcitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	12.0 – 18.0	€ 1,200 – € 1,800
Maintenance treatment with avelumab					
Avelumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	14.1 – 18.1	€ 1,410 – € 1,810

b) Adults with unresectable or metastatic urothelial carcinoma who are not eligible for a cisplatin-based therapy; first-line treatment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Enfortumab vedotin in combination with pembrolizumab	
Enfortumab vedotin	€ 91,404.29
Pembrolizumab	€ 90,059.96
Total	€ 181,464.25
Appropriate comparator therapy:	
Carboplatin in combination with gemcitabine in accordance with Annex VI to Section K of the Pharmaceuticals Directive followed by avelumab as maintenance treatment (maintenance treatment with avelumab only for patients who are progression-free)	
Carboplatin	€ 1,268.44 – € 1,902.66
Gemcitabine	€ 1,470.24 – € 2,205.36
Total	€ 2,738.68 – € 4,108.02
Maintenance treatment with avelumab	
Avelumab	€ 53,862.26 (after 6 cycles of induction therapy) – € 63,311.78 (after 4 cycles of induction therapy)
Carboplatin and gemcitabine including subsequent maintenance treatment with avelumab	
Total	€ 57,970.28 (after 6 cycles of induction therapy) – € 66,050.46 (after 4 cycles of induction therapy)

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 March 2025)

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Enfortumab vedotin in combination with pembrolizumab					
Enfortumab vedotin	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	2	34.8	€ 3,480
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	17.4 (21-day) or 8.7 (42-day)	€ 1,740 (21-day) or € 870 (42-day)
Appropriate comparator therapy					
Carboplatin in combination with gemcitabine					
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	4.0 – 6.0	€ 400 – € 600
Gemcitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	8.0 – 12.0	€ 800 – € 1,200
Maintenance treatment with avelumab					
Avelumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	17.1 – 20.1	€ 1,710 – € 2,010

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:

a) Adults with unresectable or metastatic urothelial carcinoma who are eligible for a cisplatin-based therapy; first-line treatment

The following medicinal products with new active ingredients that can be used in a combination therapy with enfortumab vedotin in the therapeutic indication of the resolution on the basis of the marketing authorisation under Medicinal Products Act are named (active ingredients and invented names) in accordance with Section 35a, paragraph 3, sentence 4 SGB V:

– Pembrolizumab (Keytruda)

b) Adults with unresectable or metastatic urothelial carcinoma who are not eligible for a cisplatin-based therapy; first-line treatment

The following medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product in the therapeutic indication of the present resolution on the basis of the marketing authorisation under Medicinal Products Act are excluded from the designation, as the G-BA has identified at least considerable additional benefit for the combination with the assessed medicinal product in the present resolution:

– Pembrolizumab (Keytruda)

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. **In Annex XIIa of the Pharmaceuticals Directive, the following information shall be added in alphabetical order:**

"Active ingredient of the assessed medicinal product

Enfortumab vedotin

Resolution according to Section 35a paragraph 3 SGB V from

3 April 2025

Therapeutic indication of the resolution

Padcev, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy.

Patient group a

Adults with unresectable or metastatic urothelial carcinoma who are eligible for a cisplatin-based therapy; first-line treatment

Naming of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V (active ingredients and invented names[2])

Pembrolizumab (Keytruda)

Period of validity of the designation

Since 3 April 2025

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.

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 3 April 2025.

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

Berlin, 3 April 2025

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

Prof. Hecken