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
Enfortumab Vedotin (urothelial cancer, pretreated with platinum-containing chemotherapy and PD-(L)1 Inhibitor)

of 1 December 2022

At its session on 1 December 2022, 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 shall be amended in alphabetical order to include the active ingredient Enfortumab Vedotin as follows:

Enfortumab Vedotin

Resolution of: 1 December 2022
Entry into force on: 1 December 2022
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 13 April 2022):

Padcev as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1 inhibitor

Therapeutic indication of the resolution (resolution of 1 December 2022):

See therapeutic indication according to marketing authorisation.

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

a) Adults with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and who are eligible for chemotherapy

Appropriate comparator therapy:

Chemotherapy according to doctor's instructions

Extent and probability of the additional benefit of enfortumab vedotin compared to chemotherapy according to doctor's instructions:

Hint for a considerable additional benefit

b) Adults with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and who are ineligible for chemotherapy

Appropriate comparator therapy:

- Best supportive care

Extent and probability of the additional benefit of enfortumab vedotin compared to the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Adults with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and who are eligible for chemotherapy

Hint for 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	↔	No relevant differences for the benefit assessment.
Health-related quality of life	↑	Advantages in the functional scales of global health status, physical functioning, role functioning and emotional functioning.
Side effects	↔	No relevant differences for the benefit assessment.
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.c.: not calculable		

EV-301 study:

- Study design: RCT, open-label, parallel
- Comparison: Enfortumab vedotin **vs** docetaxel or vinflunine or paclitaxel, at the discretion of the treating physician
- Data cut-offs:

  1st data cut-off from 15.07.2020 (overall survival, morbidity, health-related quality of life and side effects)

  2nd data cut-off from 30.07.2021 (overall survival and side effects)

[1] Data from the dossier assessment of the IQWiG (A22-61) and from the addendum (A22-107), unless otherwise indicated.

Mortality

Endpoint	Enfortumab vedotin		Chemotherapy according to doctor's instructions[a]		Enfortumab vedotin vs chemotherapy according to doctor's instructions
	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 (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[b]
Mortality					
Overall survival (2nd data cut-off from 30.07.2021)	301	12.91 [11.01; 14.92] *207 (68.8)*	307	8.94 [8.25; 10.25] *237 (77.2)*	0.70 [0.58; 0.85] 0.001 AD = +3.97 months

Morbidity

Endpoint	Enfortumab vedotin		Chemotherapy according to doctor's instructions[a]		Enfortumab vedotin vs chemotherapy according to doctor's instructions
	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 (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[b]
Progression-free survival 1 (PFS1)[c]					
1st data cut-off from 15.07.2020	301	5.55 [5.32; 5.82] *201 (66.8%)*	307	3.71 [3.52; 3.94] *231 (75.2%)*	0.62 [0.51; 0.75] < 0.0001 AD = +1.84 months
2nd data cut-off from 30.07.2021	301	5.55 [5.32; 6.28] *231 (76.7%)*	307	3.71 [3.52; 3.94] *248 (80.8%)*	0.63 [0.53; 0.76] < 0.0001 AD = +1.84 months

Endpoint	Enfortumab vedotin		Chemotherapy according to doctor's instructions[a]		Enfortumab vedotin vs chemotherapy according to doctor's instructions
	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 (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[b]
EORTC QLQ-C30 (1st data cut-off from 15.07.2020)[d]					
Fatigue	301	0.76 [0.59; 0.89] *197 (65.4)*	307	0.72 [0.49; 0.82] *180 (58.6)*	0.88 [0.71; 1.09] 0.226
Nausea and vomiting	301	1.71 [1.41; 2.37] *140 (46.5)*	307	1.28 [0.99; 1.87] *141 (45.9)*	0.83 [0.65; 1.05] 0.121
Pain	301	1.08 [0.95; 1.54] *165 (54.8)*	307	1.08 [0.95; 1.38] *159 (51.8)*	0.87 [0.69; 1.09] 0.220
Dyspnoea	301	4,44 [1,71; n.c.] *118 (39.2)*	307	1.94 [1.51; 2.60] *130 (42.3)*	0.78 [0.61; 1.01] 0.055
Insomnia	301	1.81 [1.05; 2.60] *139 (46.2)*	307	1.48 [1.08; 2.33] *134 (43.6)*	0.85 [0.67; 1.09] 0.194
Appetite loss	301	1.08 [0.82; 1.51] *164 (54.5)*	307	1.15 [0.99; 1.71] *142 (46.3)*	1.00 [0.80; 1.26] 0.969
Constipation	No usable data available[e]				
Diarrhoea	301	2.14 [1.45; 7.49] *129 (42.9)*	307	2.79 [1.58; 7.69] *114 (37.1)*	1.01 [0.78; 1.30] 0.938
Health status (EQ-5D VAS, 1st data cut-off from 15.07.2020)[f]					
	301	2.53 [1.68; 5.52] *132 (43.9)*	307	2.10 [1.51; 2.53] *136 (44.3)*	0.79 [0.62; 1.01] 0.069

Health-related quality of life

Endpoint	Enfortumab vedotin		Therapy according to doctor's instructions[a]		Enfortumab vedotin vs therapy according to doctor's instructions
	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 (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[b]
EORTC QLQ-C30 (1st data cut-off from 15.07.2020)[g]					
Global health status	301	1.41 [1.02; 1.91] *162 (53.8)*	307	0.99 [0.79; 1.18] *156 (50.8)*	0.79 [0.63; 0.99] 0.046 AD = +0.42 months
Physical functioning	301	1.87 [1.25; 2.66] *153 (50.8)*	307	1.45 [1.12; 1.68] *151 (49.2)*	0.78 [0.62; 0.99] 0.041 AD = +0.42 months
Role functioning	301	0.99 [0.79; 1.38] *174 (57.8)*	307	0.79 [0.72; 0.99] *175 (57.0)*	0.76 [0.62; 0.95] 0.015 AD = +0.20 months
Emotional functioning	301	5.45 [2.46; 6.54] *116 (38.5)*	307	2.43 [1.48; 4.17] *124 (40.4)*	0.73 [0.56; 0.95] 0.019 AD = +3.02 months
Cognitive functioning	301	1.71 [1.28; 2.20] *155 (51.5)*	307	1.45 [1.02; 1.64] *143 (46.6)*	0.91 [0.72; 1.14] 0.401
Social functioning	301	1.02 [0.79; 1.41] *167 (55.5)*	307	0.89 [0.76; 1.08] *156 (50.8)*	0.87 [0.69; 1.09] 0.203

Side effects[h]

Endpoint	Enfortumab vedotin		Therapy according to doctor's instructions[a]		Enfortumab vedotin vs therapy according to doctor's instructions
	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 (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[b]
Total adverse events (presented additionally)					
	296	0.20 [0.16; 0.23] 290 (98.0)	291	0.13 [0.10; 0.16] 288 (99.0)	-
Serious adverse events (SAE)					
	296	14,36 [5,45; n.c.] *143 (48.3)*	291	n.a. [5,26; n.c.] *135 (46.4)*	0.94 [0.75; 1.20] 0.643
Severe adverse events[i]					
	296	1.77 [1.28; 2.27] *216 (73.0)*	291	1.41 [0.95; 2.14] *200 (68.7)*	0.96 [0.79; 1.17] 0.734
Discontinuation due to AEs					
	296	n.a. *62 (20.9)*	291	n.a. *61 (21.0)*	0.93 [0.65; 1.33] 0.697
Specific adverse events					
Constipation	No usable data available				
Peripheral neuropathy (SMQ, AEs)	296	5.68 [4.63; 8.34] *153 (51.7)*	291	n.a. *104 (35.7)*	1.40 [1.09; 1.81] 0.008
Febrile neutropenia (PT, severe AEs[i])	296	n.a. *4 (1.4)*	291	n.a. *16 (5.5)*	0.23 [0.08; 0.70] 0.005
Hyperglycaemia (PT, severe AEs[i])	296	n.a. *21 (7.1)*	291	n.a. *3 (1.0)*	6.93 [2.07; 23.25] < 0.001
Eye disorders (SOC, AEs)	296	n.a. *86 (29.1)*	291	n.a. *26 (8.9)*	3.67 [2.36; 5.70] < 0.001

Endpoint	Enfortumab vedotin		Therapy according to doctor's instructions[a]		Enfortumab vedotin vs therapy according to doctor's instructions
	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 (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[b]
Gait disorder (PT, AEs)	296	n.a. *10 (3.4)*	291	n.a. *0 (0)*	n.c. 0.004
Myalgia (PT, AEs)	296	n.a. *15 (5.1)*	291	n.a. *35 (12.0)*	0.40 [0.22; 0.73] 0.002
Dysgeusia (PT, AEs)	296	n.a. *75 (25.3)*	291	n.a. *24 (8.2)*	3.28 [2.07; 5.21] < 0.001
Acute kidney injury (PT, SAEs)	296	n.a. *20 (6.8)*	291	n.a. *9 (3.1)*	2.17 [0.99; 4.77] 0.048
Blood and lymphatic system disorders (SOC, severe AEs)[j]	296	n.a. *32 (10.8)*	291	n.a. *71 (24.4)*	0.38 [0.25; 0.58] < 0.001
Nervous system disorders (SOC, severe AEs[i])[k]	296	n.a. *32 (10.8)*	291	n.a. *14 (4.8)*	2.03 [1.08; 3.82] 0.026
Skin and subcutaneous tissue disorders (SOC, SAEs)	296	n.a. *14 (4.7)*	291	n.a. *1 (0.3)*	14.23 [1.87; 108.27] < 0.001
Infections and infestations (SOC, severe AEs[i])[l]	296	n.a. *58 (19.6)*	291	n.a. *35 (12.0)*	1.62 [1.07; 2.47] 0.022
Investigations (SOC, severe AEs[i])[m]	296	n.a. *46 (15.5)*	291	n.a. *64 (22.0)*	0.61 [0.42; 0.90] 0.012

Endpoint	Enfortumab vedotin		Therapy according to doctor's instructions[a]		Enfortumab vedotin vs therapy according to doctor's instructions
	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 (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[b]

a In the EV-301 study, the chemotherapies vinflunine, paclitaxel and docetaxel were available.
b Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
c Information from the dossier of the pharmaceutical company
d Time to first deterioration; an increase in score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100)
e the results on constipation are not usable
f Time to first deterioration; an increase in score by ≥ 15 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100)
g Time to first deterioration; a decrease in score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100)
h including events due to progression of the underlying disease
i operationalised as CTCAE grade ≥ 3
j including the PTs "anaemia", "febrile neutropenia" and "neutropenia" as the most frequent symptoms
k including "peripheral sensory neuropathy" as the most frequent symptom
l including the PTs "pneumonia" and "bacterial urinary tract infection" as the most frequent symptoms
m including the PTs "neutropenia" and "leukopenia" as the most frequent symptoms

Abbreviations used:
AD = absolute difference; 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.a. = not achieved; PT = preferred term; SOC = system organ class; SAE: serious adverse event; AE: adverse event; VAS = visual analogue scale; vs = versus

Study results according to endpoints:[2]

b) Adults with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and who are ineligible for chemotherapy

An additional benefit is not proven.

[2] Data from the dossier assessment of the IQWiG (A22-61) and from the addendum (A22-107), unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	There are no usable data for the benefit assessment.
Morbidity	∅	There are no usable data for the benefit assessment.
Health-related quality of life	∅	There are no usable data for the benefit assessment.
Side effects	∅	There are no usable data for the benefit assessment.

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.c.: not calculable

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

a) Adults with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and who are eligible for chemotherapy

approx. 190 - 590 patients

b) Adults with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and who are ineligible for chemotherapy

approx. 220 - 660 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: 5 September 2022):

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

Therapy with enfortumab vedotin should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, who are experienced in the treatment of patients with locally advanced or metastatic urothelial cancer as well as specialists in urology, and other specialists participating in the Oncology Agreement.

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

The costs for the first year of treatment are presented.

Annual treatment costs:

a) Adults with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and who are eligible for chemotherapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Enfortumab vedotin	€ 141,589.50 - € 198,225.30
Appropriate comparator therapy:	
Chemotherapy according to doctor's instructions[a]	
Vinflunine	
Vinflunine	€ 71,224.29
Cisplatin in combination with gemcitabine	
Cisplatin	€ 1,506.05
Gemcitabine	€ 7,014.54
Cisplatin + gemcitabine	€ 8,520.59
Additionally required SHI costs	€ 242.72 - € 311.31
[a] The active ingredients docetaxel and paclitaxel are suitable comparators for the present benefit assessment in the context of a chemotherapy according to doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, and therefore, no costs are presented for these medicinal products.	

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 November 2022)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Enfortumab vedotin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	39	€ 3,900.00
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	13.0	€ 1,300.00
Gemcitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	39	€ 3,900.00
Vinflunine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740.00

b) Adults with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and who are ineligible for chemotherapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Enfortumab vedotin	€ 141,589.50 - € 198,225.30
Best supportive care	Different from patient to patient
Appropriate comparator therapy:	
Best supportive care	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 November 2022)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Enfortumab vedotin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	39	€ 3,900.00

5. Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with enfortumab vedotin

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients which, on the basis of the marketing authorisation under Medicinal Products Act, can be used in a combination therapy with enfortumab vedotin for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor:

a) Adults with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and who are eligible for chemotherapy

No active ingredient that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

b) Adults with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and who are ineligible for chemotherapy

No active ingredient that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 1 December 2022.

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

Berlin, 1 December 2022

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

Prof. Hecken