Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) 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

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the active ingredient enfortumab vedotin in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA is 1 June 2022. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 24 May 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 September 2022, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of enfortumab vedotin compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the

statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of enfortumab vedotin.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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

2.1.1 Approved therapeutic indication of Enfortumab Vedotin (Padcev) according to the product information

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 01.12.2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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 are eligible for chemotherapy

Appropriate comparator therapy:

- Chemotherapy according to doctor's instructions

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

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the (G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. In addition to enfortumab vedotin, medicinal products with the active ingredients cisplatin, doxorubicin, methotrexate, gemcitabine, vinflunine, pembrolizumab, atezolizumab and nivolumab are approved in the present therapeutic indication.

On 2. Non-medicinal treatment options are not considered as an appropriate comparator therapy in the present therapeutic indication. In determining the appropriate comparator therapy, it was assumed that the intended therapeutic indication includes patients with unresectable locally advanced or metastatic urothelial cancer.

On 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Pembrolizumab: Resolutions of 16 March 2018, 2 August 2018, 20 June 2019 and 5 March 2020
- Atezolizumab: Resolutions of 16 March 2018, 2 August 2018 and 20 June 2019
- Nivolumab: Resolution of 21 December 2017

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the “Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V”.

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V (see “Information on Appropriate Comparator Therapy”).

Among the approved active ingredients listed under 1., only certain active ingredients will be included in the appropriate comparator therapy, taking into account the

evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

Overall, there are limited therapy recommendations for third-line therapy for patients who have received prior treatments with platinum-containing chemotherapy and with a PD-1 or PD-L1 inhibitor.

The present guidelines mention various treatment options.[2,3,4]

The EAU guidelines agree on vinflunine as a potential treatment option, which is also approved for the present treatment setting. Alternatively, the EAU guidelines also refer to the use of taxanes, especially paclitaxel or docetaxel.

In the statements on the present benefit assessment, the clinical experts also mention that taxanes are used in clinical care.

Paclitaxel and docetaxel are not approved for the present indication. There is a discrepancy between medicinal products approved in the indication and those used in healthcare/ recommended in guidelines.

Furthermore, the available evidence also shows the importance of a platinum-containing re-exposure, whereby reference is made to the approved combination of cisplatin and gemcitabine. When renewing therapy with cisplatin and gemcitabine, the response and tolerability to prior therapy should be taken into account.

The present therapeutic indication also includes patients for whom further cytotoxic chemotherapy is not indicated. This may be the case in particular due to a deteriorated general condition. According to the current state of medical knowledge, there is no specific standard therapy for this group of patients. Treatment is individualised for each patient to alleviate symptoms and improve quality of life (best supportive care).

Overall, the G-BA therefore determines chemotherapy as the appropriate comparator therapy in the present therapeutic indication for patient group a) according to the doctor's instructions.

In total, the G-BA designates the following comparators within the framework of chemotherapy according to the doctor's instructions:

- Vinflunine

- Docetaxel

- Paclitaxel

- Cisplatin in combination with gemcitabine.

For patient group b), best supportive care is determined as the appropriate comparator therapy. Best Supportive Care (BSC) is understood as the therapy that ensures the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

---

[2] European Association of Urology (EAU) 2021; EAU guidelines on upper urinary tract urothelial carcinoma.

[3] NCCN, 2021 Bladder Cancer, Version 3.2021

[4] Oncology guideline programme, 2020 AWMF, German Cancer Society (DKG) and German Cancer Aid Foundation (DKH) S3 Guideline Early Detection, Diagnosis, Therapy and After-care of Urinary Bladder Cancer

Change of the appropriate comparator therapy:

Originally, the appropriate comparator therapy for patient group a) was determined as follows:

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

   – Vinflunine monotherapy

   or

   – Cisplatin in combination with gemcitabine

Within the framework of the written statement procedure, the clinical experts explained that treatment with taxanes (docetaxel and paclitaxel) is also considered to be of relevant importance in healthcare.

In view of the statements of the clinical experts, it is now considered appropriate by the G-BA for the present assessment to include docetaxel and paclitaxel as a treatment option in the context of chemotherapy according to the doctor's instructions.

This change in the appropriate comparator therapy has the consequence that the data on the total population of the EV-301 study, in which docetaxel or paclitaxel is also a comparator therapy in addition to vinflunine, will be used for patient group a) .

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of enfortumab vedotin is assessed as follows:

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

Justification:

The pharmaceutical company submitted results from the multicentre, open-label, randomised EV-301 study for the benefit assessment.

The study includes the intervention arm with enfortumab vedotin and the comparator arm with chemotherapy according to the doctor's instructions, selecting vinflunine, paclitaxel and docetaxel as monotherapy in each case. The currently ongoing study began in June 2018 and is being conducted in 158 study sites in North and South America, Europe, Asia and Australia.

A total of 608 adult patients with locally advanced or metastatic urothelial cancer who were pretreated with a platinum-based chemotherapy (cisplatin or carboplatin) and a PD-1 or PD-L1 inhibitor for advanced or metastatic disease and had an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1 were enrolled in the study.

Patients were randomised in a 1:1 ratio to the enfortumab vedotin arm (n = 301) or the control arm (n = 307). This was stratified by region (Western Europe vs United States vs rest of the world), ECOG-PS (0 vs 1) and the presence of liver metastases at baseline (yes vs no).

In both study arms, treatment was largely in accordance with the instructions in the respective product information. There are limitations due to the possible 3rd dose adjustment of enfortumab vedotin - which is not provided for in the study protocol - or lack of constipation prophylaxis during vinflunine treatment. Treatment in the study arms should continue until at least one of the following therapy discontinuation criteria occurs: Disease progression, initiation of new cancer therapy, withdrawal of consent, doctor's decision, death or unacceptable toxicity. A switch from the treatment of the control arm to the enfortumab vedotin arm (treatment switching) was possible after the 1st data cut-off.

Data cut-offs

2 data cut-offs are available. The first data cut-off from 15.07.2020 was planned as a predefined interim analysis and carried out as a primary analysis as recommended by the IDMC (Independent Data Monitoring Centre). Analyses of all patient-relevant endpoints (overall survival, morbidity, health-related quality of life and side effects) are available for this data cut-off. The second data cut-off from 30.07.2021 was conducted as the originally planned final analysis on overall survival at the request of the Swiss regulatory authority. Analyses on overall survival and side effects are available for this data cut-off.

For the endpoints of morbidity and health-related quality of life, the pharmaceutical company does not submit analyses for the second data cut-off. This is improper, as according to the dossier template, evaluations for all endpoints should have been conducted for this data cut-

off and submitted for the benefit assessment. It remains uncertain whether the survey for the morbidity endpoints was discontinued after the first data cut-off.

However, treatment of the majority of patients was discontinued as early as the first data cut-off. Based on the study design, it can also be assumed that for most patients who discontinued therapy before the first data cut-off, all data collected on these endpoints were available at the first data cut-off. Furthermore, a strongly decreasing response to the questionnaires EORTC QLQ-C30 and the EQ-5D can be observed as early as the first data cut-off. Overall, it is therefore not assumed that the results for the endpoints on morbidity and health-related quality of life would change to a relevant extent when considering the second data cut-off, so that the analyses for the first data cut-off are used.

For the benefit assessment, the results of the first data cut-off are used for the endpoints of morbidity and health-related quality of life, and the results of the second data cut-off are used for overall survival and the endpoints of side effects.

Extent and probability of the additional benefit

Mortality

Overall survival was operationalised in the EV-301 study as the time between randomisation and death from any cause.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of enfortumab vedotin compared to chemotherapy according to doctor's instructions. The extent of the prolongation of survival time is assessed as a significant improvement.

For the endpoint, there is an effect modification due to the sex characteristic. There was a statistically significant difference to the advantage of enfortumab vedotin for men. In contrast, there was no statistically significant difference between the treatment arms for women.

The observed effect modification due to the sex characteristic is considered insufficient to derive corresponding separate statements on the additional benefit in the overall assessment.

Morbidity

Symptomatology (EORTC QLQ-C30)

The symptomatology of the EV-301 study patients is assessed using the symptom scales of the EORTC QLQ-C30 questionnaire.

The pharmaceutical company submitted responder analyses for the percentage of patients with a deterioration of ≥ 10 points and ≥ 15 points (respective scale range 0 to 100). For the benefit assessment, the responder analyses with a response threshold of 10 points are used.

The results for the symptom scale "constipation" are not usable. There are uncertainties regarding the use of medicinal products against constipation and it is unclear to what extent

the cases of constipation that occurred in the study, some of which were severe, could have been avoided by prophylaxis.

For the endpoints assessed with the EORTC QLQ-C30, there is no statistically significant difference between the treatment arms. However, for the endpoint "appetite loss", there is an effect modification due to the sex characteristic. There was a statistically significant difference to the advantage of enfortumab vedotin for women compared to chemotherapy according to doctor's instructions. In contrast, there was no statistically significant difference between the treatment arms for men.

Health status (EQ-5D VAS)

The health status of the patients in the EV-301 study is assessed using EQ-5D VAS. The pharmaceutical company submits responder analyses for the percentage of patients with a deterioration of ≥ 7 points, ≥ 10 points and ≥ 15 points (scale range 0 to 100). For the benefit assessment, the responder analyses with a response threshold of 15 points are used.

There is no statistically significant difference between the treatment arms.

In the overall analysis of the results, there is no statistically significant difference between the treatment arms with regard to morbidity.

Health-related quality of life

The quality of life of the EV-301 study patients is assessed using the functional scales of the EORTC QLQ-C30 questionnaire.

The pharmaceutical company submitted responder analyses for the percentage of patients with a deterioration of ≥ 10 points and ≥ 15 points (respective scale range 0 to 100). For the benefit assessment, the responder analyses with a response threshold of 10 points are used.

Overall, for the functional scales of global health status, physical functioning, role functioning and emotional functioning, there was a statistically significant difference to the advantage of enfortumab vedotin compared to chemotherapy according to doctor's instructions. There is an effect modification here due to the age characteristic for the functional scale of global health status. For patients ≥ 65 years, there is a statistically significant difference to the advantage of enfortumab vedotin compared to chemotherapy according to doctor's instructions. For patients < 65 years, there is no statistically significant difference between the treatment arms.

In terms of quality of life, an overall advantage of enfortumab vedotin compared to chemotherapy according to doctor's instructions can thus be found.

Side effects

Adverse events (AEs) in total

In the EV-301 study, AEs occurred in both treatment arms in almost all participants. The results were only presented additionally.

SAEs and severe AEs

In addition to evaluations on the overall rates of SAEs and severe AEs, the pharmaceutical company additionally submits non-pre-specified evaluations excluding system organ classes

(SOC) and PTs. The pre-specified evaluations are used for the benefit assessment, as the selection presented also contains events that cannot be clearly attributed to the progression of the underlying disease.

In terms of the endpoints of SAEs and severe AEs, there is no statistically significant difference between the treatment arms.

Discontinuation due to AEs

For the endpoint of discontinuation due to AEs, no statistically significant difference was detected between the treatment arms.

Specific AEs

Constipation

For the endpoint of constipation, there are no usable data for a comparison of enfortumab vedotin with chemotherapy according to doctor's instructions.

Febrile neutropenia (SAEs)

For the endpoint of febrile neutropenia (SAEs), there is a statistically significant difference to the advantage of enfortumab vedotin compared to chemotherapy according to doctor's instructions. There is an effect modification due to the sex characteristic: For men, there is a statistically significant difference to the advantage of enfortumab vedotin compared to chemotherapy according to doctor's instructions. For women, there is no statistically significant difference between the treatment arms.

Blood and lymphatic system disorders (severe AEs)

For the endpoint of blood and lymphatic system disorders (severe AEs), there was a statistically significant difference to the advantage of enfortumab vedotin compared to chemotherapy according to doctor's instructions with an effect modification due to the age characteristic: Patients ≥ 65 years of age show a statistically significant difference to the advantage of enfortumab vedotin compared to chemotherapy according to doctor's instructions. For patients < 65 years, there is no statistically significant difference between the treatment arms.

Investigations (severe AEs)

For the endpoint of investigations (severe AEs), there was a statistically significant difference to the advantage of enfortumab vedotin compared to chemotherapy according to doctor's instructions. There is an effect modification due to the liver metastases characteristic. Here, for patients without liver metastases, there is a statistically significant difference to the advantage of enfortumab vedotin compared to chemotherapy according to doctor’s instructions. For patients with liver metastases, there is no statistically significant difference between the treatment arms.

Other specific AEs

For the endpoint of myalgia (AEs), there is a statistically significant difference to the advantage of enfortumab vedotin compared to chemotherapy according to doctor's instructions.

For the endpoints of peripheral neuropathy (AE), hyperglycaemia (severe AEs), eye disorders (AEs), gait disorder (AEs), dysgeusia (AEs), acute kidney injury (SAE), nervous system disorders (severe AEs), skin and subcutaneous tissue disorders (SAEs) and infections and infestations (severe AEs), there are statistically significant differences to the disadvantage of enfortumab vedotin compared to chemotherapy according to doctor's instructions.

In the overall assessment of the results on side effects, no relevant difference can be observed for enfortumab vedotin compared to chemotherapy according to doctor's instructions for the overall rates of severe adverse events (CTCAE grade ≥ 3) and serious adverse events. In detail, there are both advantages and disadvantages in the specific adverse events for enfortumab vedotin.

Effect modifications

Effect modifications result for a large number of endpoints:

For the endpoints of overall survival, appetite loss and febrile neutropenia (SAEs), there was an effect modification due to the sex characteristic.

For the endpoints of global health status and diseases of the blood and lymphatic system disorders (severe AEs), there was an effect modification due to the age characteristic, and for the endpoint of investigations (severe AEs), there was an effect modification due to the liver metastases characteristic.

Overall, however, it remains unclear to what extent the different subgroups overlap, so that the derivation of an additional benefit is not done separately according to subgroups.

Overall assessment

For the benefit assessment of enfortumab vedotin for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor, results of the EV-301 study are available for the endpoint categories of mortality, morbidity, health-related quality of life and side effects in comparison with chemotherapy according to doctor’s instructions.

Enfortumab vedotin leads to a statistically significant prolongation of overall survival compared to chemotherapy according to doctor's instructions. The prolongation of survival time is assessed as a significant improvement in its extent.

For the endpoints assessed with the EORTC QLQ-C30, there is no statistically significant difference between the treatment arms.

In the functional scales of the EORTC QLQ-C30, a statistically significant difference was found for global health status, physical functioning, role functioning and emotional functioning to the advantage of enfortumab vedotin compared to chemotherapy according to doctor's instructions. In the overall assessment, an advantage is found for enfortumab vedotin with regard to quality of life.

In the overall assessment of the results on side effects, no relevant difference can be observed for enfortumab vedotin compared to chemotherapy according to doctor's instructions for the overall rates of severe adverse events (CTCAE grade ≥ 3) and serious adverse events. In detail, there are both advantages and disadvantages in the specific AEs for enfortumab vedotin.

The overall assessment identifies a considerable additional benefit of enfortumab vedotin compared to chemotherapy according to doctor's instructions for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the open-label, randomised, phase III EV-301 study.

For the endpoints of overall survival, SAEs and severe AEs, the risk of bias at study level is rated as low.

For the results of the endpoints of symptomatology and health-related quality of life, the risk of bias is classified as high due to the open-label study design with subjective endpoint survey and the strongly decreasing response to questionnaires in the course of the study.

In addition, several endpoints show an effect modification due to the sex characteristic. In particular, the effect modification due to the sex characteristic for the endpoint of overall survival results in a relevant uncertainty as to the extent to which it can be assumed that the extent of the identified additional benefit is applicable to the overall patient population.

Thus, the present data basis has assessment-relevant uncertainties, which lead to a downgrading of the reliability of data for the overall assessment. Therefore, the reliability of data for the additional benefit determined is classified in the category “hint”.

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.

Justification:

For adults with locally advanced or metastatic urothelial carcinoma who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and who are ineligible for chemotherapy, the pharmaceutical company does not submit any data for the assessment of additional benefit. Therefore, an additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Padcev with the active ingredient enfortumab vedotin.

The active ingredient enfortumab vedotin is approved as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor.

In the therapeutic indication under consideration, 2 patient groups were distinguished and the appropriate comparator therapy was determined as follows:

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

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

The assessment is based on the EV-301 study, which investigated enfortumab vedotin compared to chemotherapy according to doctor's instructions, selecting vinflunine, paclitaxel and docetaxel.

On a)

For the assessment of the additional benefit of enfortumab vedotin, results of the EV-301 study are available for the endpoint categories of mortality, morbidity, health-related quality of life and side effects compared to chemotherapy according to doctor's instructions.

Enfortumab vedotin leads to a statistically significant prolongation of overall survival compared to chemotherapy according to doctor's instructions.

For the endpoint category of morbidity, there is no difference between the treatment arms. For the endpoint category of quality of life, there is an advantage of enfortumab vedotin.

In the overall assessment of the results on side effects, there is no relevant difference for enfortumab vedotin compared to chemotherapy according to doctor's instructions.

The overall assessment identifies a considerable additional benefit of enfortumab vedotin compared to chemotherapy according to doctor's instructions for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor.

In particular, the effect modification due to the sex characteristic for the endpoint of overall survival results in a relevant uncertainty as to the extent to which it can be assumed that the extent of the identified additional benefit is applicable to the overall patient population.

The reliability of data of the additional benefit identified is classified in the "hint" category.

On b)

No data were submitted by the pharmaceutical company that would allow an assessment of the additional benefit. An additional benefit is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The information submitted by the pharmaceutical company in the dossier is subject to uncertainties. This is due to methodological weaknesses and underestimations. Uncertainties arise in particular with regard to the percentage of patients with disease progression and the derivation of the healthcare data used.

In addition, the pharmaceutical company does not divide the target population according to patient group a) and b) with regard to suitability for chemotherapy.

Based on the evidence submitted in the written statement procedure[5] and presented in the dossier, the following percentages were determined for patients who were pretreated with a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and did not receive systemic therapy:

- 34% to 59% patients who are eligible for chemotherapy
- 41% to 66% patients who are ineligible for chemotherapy

Thus, the 543 to 993 patients in the SHI target population have the following breakdown:

Patient group a)

185 to 588 patients who are eligible for chemotherapy.

Patient group b)

222 to 655 patients who are ineligible for chemotherapy.

These data are also subject to uncertainties, especially with regard to transferability to the current German healthcare context and due to the limited significance of the percentage of patients in the target population who are eligible or ineligible for chemotherapy.

2.3 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.

[5] Gomez de Liano Lista A, van Dijk N, de Velasco Oria de Rueda G et al. Clinical outcome after progressing to frontline and second-line Anti-PD-1/PD-L1 in advanced urothelial cancer. Eur Urol 2020; 77(2): 269-276.

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.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 November 2022).

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Best supportive care

The treatment costs for best supportive care are different for each individual patient.

Because best supportive care has been determined as an appropriate comparator therapy, this is also reflected in the medicinal product to be assessed.

The type and scope of best supportive care can vary depending on the medicinal product to be assessed and the comparator therapy.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Enfortumab vedotin	1x on day 1, 8 and 15 per 28-day cycle	13.0	3	39
Best supportive care	Different from patient to patient			
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				
Chemotherapy according to doctor's instructions[a]				
Vinflunine	1x on day 1 per 21-day cycle	17.4	1	17.4
Cisplatin in combination with gemcitabine				
Cisplatin	1x on day 1 or day 2 per 28-day cycle	13.0	1	13
Gemcitabine	1x on day 1, 8 and 15 per 28-day cycle	13.0	3	39
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				
Best supportive care	Different from patient to patient			

[a] The active ingredients docetaxel and paclitaxel are suitable comparators for the present benefit assessment as part 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.

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements were applied (average height: 1,72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[6].

The recommended dosage for the combination of gemcitabine and cisplatin is 1,000 mg/m² body surface area for gentamicin and 70 mg/m² body surface area for cisplatin, according to the product information for gentamicin.

The application of enfortumab vedotin is 1.25 mg/kg body weight and can be increased to a maximum of 125 mg.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Enfortumab vedotin	1.25 mg/kg = 96.3 mg – 125 mg	96.3 mg – 125 mg	5 x 20 mg – 7 x 20 mg	39	195 x 20 mg - 273 x 20 mg
Best supportive care	Different from patient to patient				
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					
Chemotherapy according to doctor's instructions[a]					
Vinflunine	320 mg/m² = 608 mg	608 mg	2 x 250 mg 3 x 50 mg	17.4	34.8 x 250 mg + 52.2 x 50 mg
Cisplatin in combination with gemcitabine					
Cisplatin	70 mg/m² BSA = 133 mg	133 mg	1 x 100 mg 1 x 50 mg	13	13 x 100 mg + 13 x 50 mg
Gemcitabine	1,000 mg/m² BSA = 1,900 mg	1,900 mg	2 x 1,000 mg	39	78 x 1,000 mg
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					

[6] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Best supportive care	Different from patient to patient				
[a] The active ingredients docetaxel and paclitaxel are suitable comparators for the present benefit assessment as part 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:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Enfortumab vedotin 20 mg	1 PCI	€ 769.87	€ 1.77	€ 42.00	€ 726.10
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Cisplatin 100 mg	1 CIS	€ 76.55	€ 1.77	€ 3.10	€ 71.68
Cisplatin 50 mg	1 CIS	€ 47.67	€ 1.77	€ 1.73	€ 44.17
Gemcitabine 1,000 mg	1 PIS	€ 102.32	€ 1.77	€ 10.62	€ 89.93
Vinflunine 250 mg	1 CIS	€ 1657.81	€ 1.77	€ 91.39	€ 1564.65
Vinflunine 50 mg	1 CIS	€ 341.40	€ 1.77	€ 18.28	€ 321.35
Best supportive care	Different from patient to patient				
Abbreviations: CIS = concentrate for the preparation of an infusion solution, PIS = powder for the preparation of an infusion solution, PCI = powder for a concentrate for the preparation of a solution for infusion					

LAUER-TAXE® last revised: 15 November 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g., regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I to the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Cost/ patient/ year
Appropriate comparator therapy							
Cisplatin							
Antiemetic treatment							
In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information does not provide any specific information why the necessary costs cannot be quantified.							
Hydration/ diuresis							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	13	€ 118.43
Sodium chloride 0.9% infusion solution, 3 l - 4.4 l/day	10 x 1000 ml INF	€ 34.68	€ 1.73	€ 1.08	€ 31.87	13	€ 124.29 - € 192.88
	10 x 500 ml INF	€ 22.72	€ 1.14	€ 0.69	€ 20.89		
Abbreviation: INF = infusion solution							

LAUER-TAXE® last revised: 15 November 2022

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

2.5 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

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 24 August 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 24 May 2022, the pharmaceutical company submitted a dossier for the benefit assessment of enfortumab vedotin to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 25 May 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient enfortumab vedotin.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 August 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 September 2022. The deadline for submitting written statements was 22 September 2022.

The oral hearing was held on 10 October 2022.

By letter dated 11 October 2022, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 11 November 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 22 November 2022, and the proposed resolution was approved.

At its session on 1 December 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	24 August 2021	Determination of the appropriate comparator therapy
Working group Section 35a	4 October 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	10 October 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18.10.2022; 01.11.2022; 15.11.2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure

Subcommittee Medicinal products	22 November 2022	Concluding discussion of the draft resolution
Plenum	1 December 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 01 December 2022

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

Prof. Hecken