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 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

Contents

1. Legal basis ... 2

2. Key points of the resolution ... 2

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy ... 3

2.1.1 Approved therapeutic indication of Enfortumab vedotin (Padcev) in accordance with the product information ... 3

2.1.2 Appropriate comparator therapy ... 4

2.1.3 Extent and probability of the additional benefit ... 8

2.1.4 Summary of the assessment ... 19

2.2 Number of patients or demarcation of patient groups eligible for treatment ... 21

2.3 Requirements for a quality-assured application ... 21

2.4 Treatment costs ... 22

2.5 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 ... 29

3. Bureaucratic costs calculation ... 32

4. Process sequence ... 32

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 all 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient enfortumab vedotin (Padcev) was listed for the first time on 1 June 2022 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 26 August 2024, enfortumab vedotin received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334 from 12.12.2008, sentence 7).

On 20 September 2024, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, No. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient enfortumab vedotin with the new

therapeutic indication in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication)

"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.".

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 January 2025 on the G-BA website (www.g-ba.de), 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) in accordance with the product information

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.[2]

Therapeutic indication of the resolution (resolution of 03.04.2025):

"see approved therapeutic indication"

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

[2] The medicinal product Padcev, in combination with pembrolizumab, is approved for the first-line treatment of patients with unresectable or metastatic urothelial cancer who are eligible for platinum. In addition, the medicinal product Keytruda with the active ingredient pembrolizumab in combination with enfortumab vedotin has been granted the marketing authorisation for patients who are ineligible for platinum.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for enfortumab vedotin in combination with pembrolizumab:

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

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

Appropriate comparator therapy for enfortumab vedotin in combination with pembrolizumab:

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)

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the

Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

On 1. In addition to enfortumab vedotin in combination with pembrolizumab, medicinal products with the active ingredients cisplatin, doxorubicin, epirubicin, methotrexate, gemcitabine, pembrolizumab (as monotherapy), atezolizumab and avelumab are approved in this therapeutic indication.

On 2. In the present therapeutic indication, a non-medicinal treatment is not considered.

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

- Pembrolizumab: resolution of 16 September 2021
- Atezolizumab: resolutions of 16 March 2018 and 20 June 2019
- Avelumab: resolution of 19 August 2021

resolution of the Federal Joint Committee (G-BA) on an amendment of the Pharmaceuticals Directive (AM-RL): Annex VI (off-label use), last revised 24 June 2023:

- Carboplatin in combination with gemcitabine for the treatment of patients with unresectable locally advanced or metastatic urothelial carcinoma if cisplatin therapy is not an option (resolution of 20 May 2021)

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".

Among the approved active ingredients listed under 1., only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of care.

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 therapeutic indication according to Section 35a, paragraph 7 SGB V.

Due to the unanimously distinct therapy recommendations for cisplatin-eligible and -ineligible patients in the available evidence, the G-BA considers it appropriate to subdivide the present therapeutic indication into 2 patient groups.

Patients who are eligible for a cisplatin-based therapy

For patients who are eligible for cisplatin-based therapy, the guidelines unanimously recommend the combination of cisplatin and gemcitabine as a standard therapy. Compared to the alternatively discussed combination of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC or high-dose MVAC with additional concomitant administration of a granulocyte-stimulating factor), the combination of cisplatin and gemcitabine is considered to have a more favourable toxicity profile according to the available evidence. In their written statement, the scientific-medical societies also recommend a combination of cisplatin and gemcitabine for patients eligible for cisplatin. According to the identified guidelines, the therapy should be carried out over 4-6 cycles.

The available evidence also mentions the combination of paclitaxel, gemcitabine and cisplatin. However, the triple combination of paclitaxel, gemcitabine and cisplatin is not determined as the appropriate comparator therapy since paclitaxel is not approved in this therapeutic indication and the available evidence does not indicate that the combination therapy of paclitaxel, gemcitabine and cisplatin is preferable to the approved combination therapy of cisplatin and gemcitabine.

Following cisplatin-based therapy, avelumab as a monotherapy is available as a therapy option for first-line maintenance treatment in adult patients with locally advanced or metastatic urothelial carcinoma who are progression-free after platinum-based chemotherapy. According to the present guidelines and written opinion of the scientific-medical societies, patients who achieve at least stable disease with platinum-based therapy should be given first-line maintenance treatment with avelumab. In their resolution of 19 August 2021, the G-BA identified in the benefit assessment a hint for a considerable additional benefit of avelumab compared to best supportive care. Avelumab as maintenance treatment for patients who are progression-free following treatment with cisplatin in combination with gemcitabine is therefore determined as part of the appropriate comparator therapy for first-line therapy.

It is assumed that patients who are not progression-free following platinum-based chemotherapy will not be treated further as part of first-line treatment.

Patients who are not eligible for a cisplatin-based therapy

With regard to the patient characteristics for this patient group, the G-BA assumes that the patients show an increased risk of cisplatin-induced side effects (e.g. pre-existing neuropathy or relevant hearing impairment, renal failure, heart failure) as part of combination therapy. For patients who are ineligible for a cisplatin-based therapy, the combination of carboplatin and gemcitabine in particular is recommended in guidelines and in the written opinion of the scientific-medical societies. Although this combination is not approved for this therapeutic indication, it can be prescribed in this off-label use in accordance with Annex VI to Section K of the Pharmaceuticals Directive. According to the identified guidelines, the therapy should be carried out over 4-6 cycles.

Following carboplatin-based therapy, avelumab as a monotherapy is available as a therapy option for first-line maintenance treatment in adult patients with locally advanced or metastatic urothelial carcinoma who are progression-free after platinum-based chemotherapy. According to the present guidelines and written opinion of the scientific-medical societies, patients who achieve at least stable disease with platinum-based therapy should be given first-line maintenance treatment with avelumab. In their resolution of 19 August 2021, the G-BA identified in the benefit assessment a hint for a considerable additional benefit of avelumab compared to best supportive care. Avelumab as maintenance treatment for patients who are progression-free following treatment with carboplatin in combination with gemcitabine is therefore determined as part of the appropriate comparator therapy for first-line therapy.

The PD-1/PD-L1 antibodies pembrolizumab and atezolizumab (each as monotherapy) are two further approved treatment options for the first-line treatment of patients who are ineligible for a cisplatin-based therapy (pembrolizumab for patients whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10; atezolizumab for patients whose tumours have PD-L1 expression ≥ 5%). In the written opinion of the scientific-medical society and the present guidelines, the use of an immune checkpoint inhibitor is only recommended for patients with PD-L1 expression who are ineligible for platinum. With regard to platinum-eligible patients, the present guidelines explain that PD1 or PD-L1 inhibitors are currently not recommended for first-line treatment, as no significant survival benefit has been shown. For both active ingredients, no additional benefit was identified in the respective benefit assessments for adults who are ineligible for a cisplatin-based therapy (G-BA resolutions of 20 June 2019 and 16 September 2021). Pembrolizumab and atezolizumab are not determined as an appropriate comparator therapy in the present case.

It is assumed that patients who are not progression-free following platinum-based chemotherapy will not be treated further as part of first-line treatment.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

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

Indication of a considerable additional benefit.

Justification:

To prove an additional benefit of enfortumab vedotin in combination with pembrolizumab for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-based therapy, the pharmaceutical company presented the dossier with the results of the 1st data cut-off from 8 August 2023 of the ongoing EV-302/KN-A39 study, which has been conducted in 183 study sites, particularly in Asia, Europe and North America, since March 2020.

The EV-302 / KN-A39 study is a randomised, controlled, open-label phase III study in which a total of 886 patients with histologically confirmed urothelial carcinoma of the bladder, renal pelvis, ureter or urethra were enrolled and randomly assigned in a 1:1 ratio to treatment with enfortumab vedotin in combination with pembrolizumab (N = 442) or cisplatin or carboplatin in combination with gemcitabine (N = 444).

Cisplatin suitability was determined in 482 patients prior to randomisation (intervention arm: n = 240, comparator arm: n = 242). In contrast, 404 patients (intervention and comparator arms: n = 202 each) were assessed as being ineligible for cisplatin, depending on glomerular filtration rate (GFR), Eastern Cooperative Oncology Group Performance Status (ECOG-PS), audiometric hearing loss and the presence of heart failure, and were assigned to treatment with carboplatin.

As part of the written statement procedure, the pharmaceutical company submitted data of the 2nd data cut-off from 8 August 2024, on which the present assessment is based.

About the implementation of the appropriate comparator therapy

For patients who are progression-free following chemotherapy, it was determined as part of the appropriate comparator therapy that maintenance treatment with avelumab should be given. However, the EV-302 / KN-A39 study did not regularly provide for maintenance treatment with avelumab in the comparator arm for patients who were progression-free following chemotherapy according to study design. Maintenance treatment with avelumab was not approved at the time of the study design. Post-authorisation of avelumab, the study protocol was amended to specify that maintenance treatment with avelumab can be used after completion or discontinuation of platinum-containing chemotherapy in accordance with the current product information and depending on the principal investigator's assessment as well as local availability.

According to the available data on the first data cut-off from the dossier of the pharmaceutical company and supplementary data submitted during the written statement procedure, 3 patient groups can be differentiated with regard to the use of avelumab in the EV-302/KN-A39 study:

1. Patients for whom maintenance treatment with avelumab was possible according to the pharmaceutical company and who received avelumab
2. Patients for whom maintenance treatment with avelumab was not possible according to the pharmaceutical company
3. Patients for whom maintenance treatment with avelumab was possible according to the pharmaceutical company, but still did not receive avelumab

According to the pharmaceutical company, the appropriate comparator therapy has been implemented in all patients who either received maintenance treatment with avelumab or for whom this was not possible for justified reasons. According to the information provided on the 2nd data cut-off for patient groups a) and b), these are around 70% of patients in the comparator arm of the relevant sub-population. However, the information provided also shows that a relevant percentage of patients did not receive maintenance treatment with avelumab, although this would have been possible and therefore also indicated.

In order to specifically address the uncertainty of the results on overall survival arising from the non-regular use of maintenance treatment with avelumab, the pharmaceutical company presented 3 sensitivity analyses and tipping point analyses (submitted as part of the statement) at the 1st data cut-off and at the 2nd data cut-off (submitted as part of the statement).

In the tipping point analyses presented with the statement, patients who were imputed as survived in sensitivity analysis 2 are successively counted as deceased at their original time of death, while the remaining patients continue to be included in the analysis as survived. According to the pharmaceutical company, death events are categorised as such in ascending order, i.e. patients with a shorter actual survival time are the first to be included in the analysis. The results of the tipping point analyses are assessed as inadequately certain and are based on unverifiable assumptions, so that they are unsuitable for quantifying the extent of the additional benefit in addition to the sensitivity analyses presented. Therefore, the results of the tipping point analyses are not used.

In the sensitivity analyses, patients who did not receive avelumab despite suitability according to the pharmaceutical company's criteria and who died were considered in different ways.

- Sensitivity analysis 1: Patients who were eligible for maintenance treatment with avelumab and who did not receive avelumab and died were censored at the time of death. This means that the observation period of these patients until death is included in the analysis without taking the event itself into account.
- Sensitivity analysis 2: Patients who were eligible for maintenance treatment with avelumab and who did not receive avelumab and died were censored at the time of the data cut-off and thus imputed as event-free (i.e. survived) up to the data cut-off.
- Sensitivity analysis 3: Patients who were eligible for maintenance treatment with avelumab and who did not receive avelumab and died are imputed with a modified time of death or censored at the time of data cut-off, depending on which event occurred earlier. In this analysis, a simplified assumption was made that the patients would have benefited from treatment with avelumab to the same extent as the pharmaceutical company’s estimate from the JAVELIN Bladder 100 study.

Sensitivity analysis 2 represents a maximum assumption, as it assumes that all patients for whom maintenance treatment with avelumab was an option according to the pharmaceutical company and who did not receive avelumab and died would instead have survived until the time of the data cut-off presented. It therefore represents the best possible result in terms of

overall survival of these patients at the present data cut-off. It is assumed that the actual result for the endpoint of overall survival would have been between the result of the main analysis (all dead) and sensitivity analysis 2 (all alive) if maintenance treatment with avelumab had been fully implemented. Sensitivity analyses 1 and 3 provide additional information on this with less extreme assumptions for the replacement or consideration of deaths in this group.

The presented sensitivity analyses 1 to 3 are suitable to adequately address the uncertainty due to the incomplete implementation of maintenance treatment with avelumab in relation to those patients who did not receive avelumab despite suitability, and died.

There are further uncertainties regarding the implementation of the maintenance treatment with avelumab. These include, for example, the lack of specific information on the use of avelumab and the lack of information on when maintenance treatment with avelumab was started after completion of chemotherapy. With regard to patients with disease progression or death within 10 weeks of the last dose of chemotherapy, there is no information on when the respective events occurred within this time frame. Therefore, it remains unclear how many patients with disease progression or death within 10 weeks of the last dose of chemotherapy would have been eligible for earlier use of maintenance treatment with avelumab, from which they would have potentially benefited.

Overall, the results of the EV-302 / KN-A39 study can be interpreted, based on the information presented by the pharmaceutical company on the implementation of maintenance treatment with avelumab and on the associated sensitivity analyses of the endpoint of overall survival despite the uncertainties described, and used for the assessment of the additional benefit.

Extent and probability of the additional benefit

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

Mortality

The overall survival was operationalised in the EV-302 / KN-A39 study as the time from randomisation to death from any cause.

Taking into account the sensitivity analyses presented, it is possible to interpret the results of the endpoint of overall survival in the present data constellation.

The main analysis showed a statistically significant difference in favour of enfortumab vedotin + pembrolizumab compared to cisplatin + gemcitabine.

The sensitivity analyses 1 and 3 presented, in which patients in the comparator arm for whom maintenance treatment with avelumab would potentially have been indicated and who died without maintenance treatment were considered differently, also showed a statistically significant difference to the advantage of enfortumab vedotin + pembrolizumab compared to cisplatin + gemcitabine. This effect is not maintained if the maximum assumption is made that all of these patients in the comparator arm would have survived until the present data cut-off (sensitivity analysis 2). Since the probability of this assumption (all patients survive until the data cut-off) continues to decrease with increasing duration of observation, i.e. for the 2nd data cut-off compared to the 1st data cut-off, this does not call into question an additional benefit in the present data basis.

Overall, the results of overall survival are considered a relevant improvement. However, the results of the main analysis and the presented 3 sensitivity analyses of overall survival differ significantly with regard to the extent of the respective effect. An additional benefit is

identified for the endpoint of overall survival, the overall extent of which cannot be quantified with certainty.

Morbidity

Progression-free survival

Progression-free survival was defined in the EV-302 / KN-A38 study as the time from randomisation to the first documentation of disease progression or death from any cause, whichever occurs first, evaluated according to RECIST (Response Evaluation Criteria In Solid Tumours, version 1.1) criteria version 1.1. by a blinded, independent, central review committee.

PFS is statistically significantly prolonged with enfortumab vedotin + pembrolizumab compared to cisplatin + gemcitabine (if applicable followed by avelumab maintenance treatment).

The present PFS endpoint is a composite endpoint consisting of endpoints from the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component "disease progression" is collected according to RECIST criteria and thus predominantly by means of imaging procedures.

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS.

The overall statement on the additional benefit remains unaffected.

Worst pain (BPI-SF item 3), pain severity (BPI-SF items 3-6) and impairment due to pain (BPI-SF items 9a-g)

For the endpoints of worst pain (BPI-SF item 3), pain severity (BPI-SF items 3-6) and impairment due to pain (BPI-SF items 9a-9g), responder analyses over the time to first deterioration by ≥ 2 points (scale range 0 to 10) are available in the dossier presented. For the endpoints of pain severity (BPI-SF items 3-6) and impairment due to pain (BPI-SF items 9a-9g), these responder analyses were unsuitable for the benefit assessment, as the response threshold of ≥ 2 points was not predefined for these endpoints and does not correspond exactly to 15% of the scale range.

In their statement, the pharmaceutical company submitted responder analyses over the time to first deterioration by ≥ 1.5 points, which corresponds to 15% of the scale range, for the endpoints of pain severity (BPI-SF items 3-6) and impairment due to pain (BPI-SF items 9a-9g).

The analyses of the endpoint of pain severity of the BPI-SF for items 3-6 are only presented additionally. In order to avoid double counting, only the worst pain and the impairment due to pain are used for the assessment.

For the endpoints of worst pain and impairment due to pain, there were no statistically significant differences between the treatment groups.

Symptomatology (EORTC QLQ-C30)

Symptomatology was assessed using the EORTC QLQ-C30 questionnaire and operationalised as time to first deterioration by ≥ 10 points.

There was no statistically significant difference between the treatment groups for each of the endpoints "Fatigue", "Pain", "Dyspnoea", "Insomnia" and "Diarrhoea".

The symptom scales "Nausea and vomiting", "Appetite loss" and "Constipation" each showed statistically significant differences in favour of enfortumab vedotin in combination with pembrolizumab.

Health status (EQ-5D VAS)

Health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire and operationalised as time to first deterioration by ≥ 15 points. However, there was no statistically significant difference between the treatment arms for this endpoint.

The overall analysis of the morbidity results showed moderate advantages in favour of enfortumab vedotin + pembrolizumab over cisplatin + gemcitabine (if applicable followed by avelumab maintenance treatment).

Health-related quality of life

EORTC QLQ-C30

Health-related quality of life was assessed using the EORTC QLQ-C30 questionnaire and operationalised as the time to first deterioration by ≥ 10 points.

There was no statistically significant difference between the treatment groups for the endpoints "Global health status", "Role functioning", "Emotional functioning" and "Cognitive functioning".

For the endpoint “Physical functioning”, there was no statistically significant difference between the treatment groups. However, there was an effect modification due to the age characteristic. There was a statistically significant difference to the advantage of enfortumab vedotin + pembrolizumab for patients < 65 years of age, while there was no statistically significant difference for patients ≥ 65 years of age.

For the endpoint "Social functioning", there was no statistically significant difference between the treatment groups. There were non-assessable effect modifications due to the age and metastases characteristics.

In view of the fact that the effect modifications shown are only evident for some endpoints, the result for the total population is used for the assessment.

Overall, there were no relevant differences for the benefit assessment in the endpoint category of health-related quality of life.

Side effects

Total adverse events (AEs)

In the EV-302/KN-A39 study, AEs occurred in both treatment arms in almost all patients. The results were only presented additionally.

Serious adverse events (SAEs) and therapy discontinuation due to AEs

For the endpoints SAEs and therapy discontinuation due to AEs, there was no statistically significant difference between the treatment arms.

Severe AEs (CTCAE grade 3-4)

For the endpoint of severe AEs, there was a statistically significant advantage in favour of enfortumab vedotin + pembrolizumab.

Specific AEs

Immune-mediated SAEs, immune-mediated severe AEs, peripheral neuropathy (AEs), skin reactions (AEs) and severe hyperglycaemia (severe AEs)

For the endpoints of immune-mediated SAEs, immune-mediated severe AEs, peripheral neuropathy (AEs), skin reactions (AEs) and severe hyperglycaemia (severe AEs), there was a statistically significant difference to the disadvantage of enfortumab vedotin + pembrolizumab compared to cisplatin + gemcitabine.

Severe nephrotoxicity (severe AEs)

For the endpoint of severe nephrotoxicity (severe AEs), there was no statistically significant difference between the treatment groups.

Other specific AEs

For the endpoints of nausea (AEs), blood and lymphatic system disorders (severe AEs), urinary tract infection (severe AEs) and general disorders and administration site conditions (severe AEs), there was a statistically significant difference to the advantage of enfortumab vedotin + pembrolizumab compared to cisplatin + gemcitabine.

For the endpoints of eye disorders (AEs), endocrine disorders (AEs), gastrointestinal disorders (SAEs), respiratory, thoracic and mediastinal disorders (SAEs), diarrhoea (severe AEs) and hepatobiliary disorders (severe AEs), there was a statistically significant difference to the disadvantage of enfortumab vedotin + pembrolizumab compared to cisplatin + gemcitabine in each case.

For the endpoint of vomiting (AEs), there was a statistically significant difference to the advantage of enfortumab vedotin + pembrolizumab compared to cisplatin + gemcitabine. There was an effect modification due to the age characteristic. There was a statistically significant advantage for patients < 65 years of age and no statistically significant difference for patients ≥ 65 years of age.

For the endpoint of ear and labyrinth disorders (AEs), there was a statistically significant difference to the advantage of enfortumab vedotin + pembrolizumab compared to cisplatin + gemcitabine. There was an effect modification due to the age characteristic. There was a statistically significant difference to the advantage of enfortumab vedotin + pembrolizumab compared to the appropriate comparator therapy for patients < 65 years of age as well as patients ≥ 65 years of age.

In view of the fact that this effect modification is only shown for some endpoints, the result for the total population is used for the assessment.

In summary, the side effects of enfortumab vedotin in combination with pembrolizumab showed an advantage for severe AEs as well as advantages and disadvantages for some specific AEs in detail.

<u>Overall assessment</u>

For the assessment of the additional benefit of enfortumab vedotin in combination with pembrolizumab in adults with unresectable or metastatic urothelial carcinoma in the first-line, the results on mortality, morbidity, health-related quality of life and side effects are available from the randomised, open-label, multicentre, controlled EV-302/KN-A39 study. The assessment is based on the relevant sub-population of patients who are eligible for a cisplatin-based therapy.

The EV-302/KN-A39 study did not regularly provide for maintenance treatment with avelumab in the comparator arm for patients who were progression-free following chemotherapy according to study design. Sensitivity analyses are available in which patients who did not receive avelumab despite suitability according to the pharmaceutical company's criteria and who died were considered in different ways. The results of the study can be interpreted, based on the information presented on the implementation of maintenance treatment with avelumab and on the associated sensitivity analyses on the endpoint of overall survival despite the uncertainties described, and used for the assessment of the additional benefit.

For the endpoint of overall survival, the main analysis and the presented sensitivity analyses 1 and 3 showed a statistically significant difference in favour of enfortumab vedotin + pembrolizumab compared to cisplatin + gemcitabine.

Overall, the results of overall survival are considered a relevant improvement. However, the results of the main analysis and the presented 3 sensitivity analyses of overall survival differ significantly with regard to the extent of the respective effect. An additional benefit is therefore to be identified for the endpoint of overall survival, the overall extent of which cannot be quantified with certainty.

With regard to the endpoint category of morbidity (assessed using BPI-SF item 3 and items 9a-9g, EORTC QLQ-C30, EQ-5D VAS), there were moderate advantages in favour of enfortumab vedotin + pembrolizumab compared to cisplatin + gemcitabine.

For health-related quality of life (assessed using the EORTC QLQ-C30), there was no relevant difference for the benefit assessment overall.

For the endpoint category of side effects, enfortumab vedotin + pembrolizumab showed an advantage for severe AEs and advantages and disadvantages for some specific AEs in detail.

The overall analysis showed positive effects on overall survival, morbidity and side effects. The advantage in overall survival is rated as a relevant improvement. However, the extent of the effect cannot be quantified with certainty in view of the uncertainties described.

In the overall assessment, a non-quantifiable additional benefit of enfortumab vedotin in combination with pembrolizumab compared with cisplatin + gemcitabine (if applicable followed by avelumab maintenance treatment) was therefore identified.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, controlled, open-label, phase III EV-302/KN-A39 study.

The cross-endpoint risk of bias of the EV-302/KN-A39 study is estimated to be low.

For the endpoint of overall survival, the risk of bias is rated to be low.

With regard to the endpoint categories of morbidity and health-related quality of life, there was an increased risk of bias in the results (collected with BPI-SF item 3, EORTC QLQ-C30 and EQ-5D VAS) due to the decreasing return rate of the respective questionnaire over the course of the study, the percentage of patients not included in the analysis (> 10%) and the difference between the treatment groups (> 5 percentage points).

The endpoint-specific risk of bias in the results on side effects is classified as high, as only the treatment with chemotherapy is shown in the comparator arm, but not the period of possible maintenance treatment with avelumab.

Overall, the available data basis is subject to uncertainties. However, these uncertainties are not rated so high as to justify a downgrading of the reliability of data of the overall assessment.

Thus, the reliability of data for the additional benefit determined in the present assessment is classified in the “indication” category.

Extent and probability of the additional benefit

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

Mortality

The overall survival was operationalised in the EV-302 / KN-A39 study as the time from randomisation to death from any cause.

Taking into account the sensitivity analyses presented, it is possible to interpret the results of the endpoint of overall survival in the present data constellation.

The main analysis showed a statistically significant difference in favour of enfortumab vedotin + pembrolizumab compared to carboplatin + gemcitabine.

The 3 sensitivity analyses presented also showed a statistically significant difference to the advantage of enfortumab vedotin + pembrolizumab compared to carboplatin + gemcitabine. This effect is also maintained in the sensitivity analysis 2 which is based on the maximum assumption that all of these patients in the comparator arm would have survived until the present data cut-off.

Overall, the results of overall survival are considered a significant improvement.

Morbidity

Progression-free survival

Progression-free survival was defined in the EV-302 / KN-A39 study as the time from randomisation to the first documentation of disease progression or death from any cause, whichever occurs first, evaluated according to RECIST (Response Evaluation Criteria In Solid Tumours, version 1.1) criteria version 1.1. by a blinded, independent, central review committee.

PFS is statistically significantly prolonged with enfortumab vedotin + pembrolizumab compared to carboplatin + gemcitabine (if applicable followed by avelumab maintenance treatment).

The present PFS endpoint is a composite endpoint consisting of endpoints from the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component "disease progression" is collected according to RECIST criteria and thus predominantly by means of imaging procedures.

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS.

The overall statement on the additional benefit remains unaffected.

Worst pain (BPI-SF item 3), pain severity (BPI-SF items 3-6) and impairment due to pain (BPI-SF items 9a-g)

For the endpoints of worst pain (BPI-SF item 3), pain severity (BPI-SF items 3-6) and impairment due to pain (BPI-SF items 9a-9g), responder analyses over the time to first deterioration by ≥ 2 points (scale range 0 to 10) are available in the dossier presented. For the endpoints of pain severity (BPI-SF items 3-6) and impairment due to pain (BPI-SF items 9a-9g), these responder analyses were unsuitable for the benefit assessment, as the response threshold of ≥ 2 points was not predefined for these endpoints and does not correspond exactly to 15% of the scale range.

In their statement, the pharmaceutical company submitted responder analyses over the time to first deterioration by ≥ 1.5 points, which corresponds to 15% of the scale range, for the endpoints of pain severity (BPI-SF items 3-6) and impairment due to pain (BPI-SF items 9a-9g).

The analyses of the endpoint of pain severity of the BPI-SF for items 3-6 are only presented additionally. In order to avoid double counting, only the worst pain and the impairment due to pain are used for the assessment.

For the endpoint of worst pain, there was a statistically significant difference to the advantage of enfortumab vedotin in combination with pembrolizumab. There was an effect modification due to the metastases characteristic. There was no statistically significant difference for patients with visceral metastases. For patients with only lymph node metastases, there was a statistically significant difference to the advantage of enfortumab vedotin + pembrolizumab compared with the appropriate comparator therapy.

In view of the fact that this effect modification is only shown for some endpoints, the result for the total population is used for the assessment.

For the endpoint of impairment due to pain, there was no difference between the treatment arms.

Symptomatology (EORTC QLQ-C30)

Symptomatology was assessed using the EORTC QLQ-C30 questionnaire and operationalised as time to first deterioration by ≥ 10 points.

For the "Fatigue" endpoint, there was no statistically significant difference between the treatment groups. However, there was an effect modification due to the sex characteristic. There was a statistically significant difference to the advantage of enfortumab vedotin + pembrolizumab for women; there was no statistically significant difference for men.

For the "Constipation" endpoint, there was a statistically significant difference to the advantage of enfortumab vedotin + pembrolizumab compared to carboplatin + gemcitabine. There was an effect modification due to the metastases characteristic. For both patients with visceral metastases and patients with only lymph node metastases, there was a statistically significant difference to the advantage of enfortumab vedotin + pembrolizumab compared with the appropriate comparator therapy.

In view of the fact that the effect modifications shown are only evident for some endpoints, the result for the total population is used for the assessment.

For the "Nausea and vomiting" endpoint, there was a statistically significant difference to the advantage of enfortumab vedotin + pembrolizumab compared to carboplatin + gemcitabine.

There was no statistically significant difference between the treatment groups for each of the endpoints "Pain", "Dyspnoea", "Insomnia", "Appetite loss" and "Diarrhoea".

Health status (EQ-5D VAS)

Health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire and operationalised as time to first deterioration by ≥ 15 points. However, there was no statistically significant difference between the treatment arms for this endpoint.

The overall analysis of the morbidity results showed moderate advantages in favour of enfortumab vedotin + pembrolizumab over carboplatin + gemcitabine (if applicable followed by avelumab maintenance treatment).

Health-related quality of life

EORTC QLQ-C30

Health-related quality of life was assessed using the EORTC QLQ-C30 questionnaire and used after operationalisation as the time to first deterioration by ≥ 10 points. There was no statistically significant difference between the treatment groups in any of the functional scales.

There was an effect modification due to the sex characteristic for the "Role functioning" and "Emotional functioning" endpoints. There was a statistically significant difference to the advantage of enfortumab vedotin + pembrolizumab in each case for women; there was no statistically significant difference in each case for men.

In view of the fact that the effect modifications shown are only evident for some endpoints, the result for the total population is used for the assessment.

Overall, there were no relevant differences for the benefit assessment in the endpoint category of health-related quality of life.

Side effects

Total adverse events (AEs)

In the EV-302 / KN-A39 study, AEs occurred in both treatment arms in almost all patients. The results were only presented additionally.

Serious adverse events (SAEs) and therapy discontinuation due to AEs

For the endpoints SAEs and therapy discontinuation due to AEs, there was no statistically significant difference between the treatment arms.

Severe AEs (CTCAE grade 3-4)

For the endpoint of severe AEs, there was a statistically significant advantage in favour of enfortumab vedotin + pembrolizumab.

Specific AEs

Immune-mediated SAEs, immune-mediated severe AEs, peripheral neuropathy (AEs), skin reactions (AEs) and severe hyperglycaemia (severe AEs)

For the endpoints of immune-mediated SAEs, immune-mediated severe AEs, peripheral neuropathy (AEs), skin reactions (AEs) and severe hyperglycaemia (severe AEs), there was a statistically significant difference to the disadvantage of enfortumab vedotin + pembrolizumab compared to carboplatin + gemcitabine.

Severe nephrotoxicity (severe AEs)

For the endpoint of severe nephrotoxicity (severe AEs), there was no statistically significant difference between the treatment groups.

Other specific AEs

For the endpoints of constipation (AEs) and blood and lymphatic system disorders (severe AEs), there was a statistically significant difference in each case to the advantage of enfortumab vedotin + pembrolizumab compared to carboplatin + gemcitabine.

For the endpoints of diarrhoea (AEs), dysgeusia (AEs), eye disorders (AEs), endocrine disorders (AEs) and acute kidney injury (severe AEs), there was a statistically significant difference in each case to the disadvantage of enfortumab vedotin + pembrolizumab compared to carboplatin + gemcitabine.

In summary, the side effects of enfortumab vedotin + pembrolizumab showed an advantage for severe AEs as well as advantages and disadvantages for some specific AEs in detail.

Overall assessment

For the assessment of the additional benefit of enfortumab vedotin in combination with pembrolizumab in adults with unresectable or metastatic urothelial carcinoma in the first-line, results on mortality, morbidity, health-related quality of life and side effects are available from the randomised, open-label, multicentre, controlled EV-302/KN-A39 study for the relevant sub-population of patients who are ineligible for a cisplatin-based therapy.

The EV-302/KN-A39 study did not regularly provide for maintenance treatment with avelumab in the comparator arm for patients who were progression-free following chemotherapy according to study design. Sensitivity analyses are available in which patients who did not receive avelumab despite suitability according to the pharmaceutical company's criteria and who died were considered in different ways. The results of the study can be interpreted, based on the information presented on the implementation of maintenance treatment with avelumab and on the associated sensitivity analyses on the endpoint of overall survival despite the uncertainties described, and used for the assessment of the additional benefit.

For the endpoint of overall survival, the main analysis and the three sensitivity analyses presented showed a statistically significant difference in favour of enfortumab vedotin + pembrolizumab compared to carboplatin + gemcitabine.

Overall, the results of overall survival are considered a significant improvement.

With regard to the endpoint category of morbidity (assessed using BPI-SF item 3 and items 9a-9g, EORTC QLQ-C30, EQ-5D VAS), there were moderate advantages in favour of enfortumab vedotin + pembrolizumab compared to carboplatin + gemcitabine.

For health-related quality of life (assessed using the EORTC QLQ-C30), there was no relevant difference for the benefit assessment overall.

For the endpoint category of side effects, enfortumab vedotin + pembrolizumab showed an advantage for severe AEs and advantages and disadvantages for some specific AEs in detail.

Overall, the G-BA concluded a considerable additional benefit of enfortumab vedotin in combination with pembrolizumab for the treatment of adults with unresectable or metastatic urothelial carcinoma in the first-line compared with carboplatin + gemcitabine (if applicable followed by avelumab maintenance treatment).

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, controlled, open-label, phase III EV-302/KN-A39 study.

The cross-endpoint risk of bias of the EV-302/KN-A39 study is estimated to be low.

The risk of bias for the results of the overall survival endpoint is classified as low.

With regard to the endpoint categories of morbidity and health-related quality of life, there was an increased risk of bias in the results (collected with BPI-SF item 3, EORTC QLQ-C30 and EQ-5D VAS) due to the decreasing return rate of the respective questionnaire over the course of the study, the percentage of patients not included in the analysis (> 10%) and the difference between the treatment groups (> 5 percentage points).

The endpoint-specific risk of bias in the results on side effects is classified as high, as only the treatment with chemotherapy is shown in the comparator arm, but not the period of possible maintenance treatment with avelumab.

Overall, the available data basis is subject to uncertainties. However, these uncertainties are not rated so high as to justify a downgrading of the reliability of data of the overall assessment. Thus, the reliability of data for the additional benefit determined in the present assessment is classified in the “indication” category.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient enfortumab vedotin:

"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."

In the therapeutic indication under consideration, the research question for the benefit assessment was based on 2 patient groups. These differ in terms of whether the patients are eligible for cisplatin or not:

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

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

For the benefit assessment, the pharmaceutical company submitted data from the EV-302 / KN-A39 study. Adults with unresectable or metastatic urothelial carcinoma in the first-line who are eligible for platinum-based therapy were enrolled in this open-label, randomised, controlled phase III study. The assessment is based on the 2nd data cut-off from 8 August 2024 of the EV-302 / KN-A39 study submitted in the written statement procedure

On a)

For adults eligible for a cisplatin-based therapy, cisplatin in combination with gemcitabine, if applicable followed by avelumab maintenance treatment, was determined to be the appropriate comparator therapy.

For the endpoint of overall survival, both the main analysis and the sensitivity analyses showed a statistically significant difference in favour of enfortumab vedotin + pembrolizumab compared to cisplatin + gemcitabine.

Overall, the prolongation of overall survival is considered a relevant improvement. However, the results of the sensitivity analyses differ significantly with regard to the extent of the respective effect. An additional benefit can therefore be identified for the endpoint of overall survival, the overall extent of which cannot be quantified with certainty.

With regard to the endpoint category of morbidity (assessed using BPI-SF item 3 and items 9a-9g, EORTC QLQ-C30, EQ-5D VAS), there were moderate advantages in favour of enfortumab vedotin + pembrolizumab compared to cisplatin + gemcitabine.

For health-related quality of life (assessed using the EORTC QLQ-C30), there was no relevant difference for the benefit assessment overall.

For the endpoint category of side effects, enfortumab vedotin in combination with pembrolizumab showed an advantage for severe AEs and advantages and disadvantages for some specific AEs in detail.

The overall analysis showed positive effects on overall survival, morbidity and side effects. The magnitude of the effect on overall survival indicates a clinically significant improvement compared with the cisplatin + gemcitabine, but this cannot be quantified with certainty against the background of the uncertainties described.

In the overall assessment, a non-quantifiable additional benefit of enfortumab vedotin in combination with pembrolizumab compared with cisplatin + gemcitabine (if applicable followed by avelumab maintenance treatment) was therefore identified.

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

On b)

For adults ineligible for a cisplatin-based therapy, carboplatin in combination with gemcitabine, if applicable followed by avelumab maintenance treatment, was determined to be the appropriate comparator therapy.

For the endpoint of overall survival, there was a statistically significant difference to the advantage of enfortumab vedotin + pembrolizumab compared to carboplatin + gemcitabine.

For the endpoint of overall survival, both the main analysis and the sensitivity analyses showed a statistically significant difference to the advantage of enfortumab vedotin + pembrolizumab compared to carboplatin + gemcitabine. Overall, the results of overall survival are considered a significant improvement.

With regard to the endpoint category of morbidity (assessed using BPI-SF item 3 and items 9a-9g, EORTC QLQ-C30, EQ-5D VAS), there were moderate advantages in favour of enfortumab vedotin + pembrolizumab compared to carboplatin + gemcitabine.

For health-related quality of life (assessed using the EORTC QLQ-C30), there was no relevant difference for the benefit assessment overall.

For the endpoint category of side effects, enfortumab vedotin + pembrolizumab showed an advantage for severe AEs and advantages and disadvantages for some specific AEs in detail.

Overall, the G-BA concluded a considerable additional benefit of enfortumab vedotin + pembrolizumab for the treatment of adults with unresectable or metastatic urothelial

carcinoma in the first-line compared with carboplatin + gemcitabine (if applicable followed by avelumab maintenance treatment).

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

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 G-BA base their resolution generally on the pharmaceutical company's information on the total population from the procedure for pembrolizumab[3].

These are however subject to uncertainties. There are both underestimating factors, such as in particular the determination of the percentage values of UICC stages including cases with an unknown stage in the upper limit, and overestimating factors, such as the implicit assumption of the pharmaceutical company that all patients are eligible for first-line systemic therapy - at least for the lower limit.

For the lower limit of patient group a), the figures from the procedure for nivolumab[4] are additionally used.

Data from the publications by Richters[5] et al. and Miloy[6] et al., which approximately reflect the German healthcare context, are used to approximate the percentage values of the individual patient groups. Accordingly, 42.7% or 64% were eligible for cisplatin, 47.4% or 18% for carboplatin and 9.8% or 19% for neither cisplatin nor carboplatin. Based on the percentages of patients examined in the study, weighted mean values are formed so that the following percentages are assumed overall and applied to the total population with a range of 1,051 to 2,597 patients:

49% patients who are eligible for cisplatin.

39% patients who are ineligible for cisplatin.

12% patients who are eligible for neither cisplatin nor carboplatin.

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: 25 March 2025):

[3] https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1132/

[4] https://www.g-ba.de/downloads/39-261-6975/2024-12-19_AM-RL-XII_Nivolumab_D-1081_BAnz.pdf

[5] Richters et al. Overall Survival of Patients Receiving Cisplatin or Carboplatin for Primary Metastatic Urothelial Carcinoma of the Bladder: A Contemporary Dutch Nationwide Cohort Study. Eur Urol Focus 2022; 8(4): 995-1002.

[6] Milloy N et al. Real-World Analysis of Treatment Patterns and Platinum-Based Treatment Eligibility of Patients With Metastatic Urothelial Cancer in 5 European Countries. J. Clin Genitourin Cancer. 2024 Feb;22(1):e136-e147.e1.

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.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 March 2025).

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

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 varies from patient to patient 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.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements of the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916)[7].

For the use of carboplatin in combination with gemcitabine in unresectable, locally advanced or metastatic urothelial carcinoma, Annex VI to Section K of the Pharmaceuticals Directive specifies a dosage of carboplatin of 4.5 x [GFR + 25] mg on day 1 and gemcitabine of 1,000 mg/m^2 body surface area on days 1 and 8 of a 21-day cycle.

The dosage of carboplatin is calculated using the Calvert formula and the estimation of renal function using the Cockcroft-Gault equation, with average height values (women: 166 cm, men: 179 cm)[7], weight (women: 69.2 kg, men: 85.8 kg)[7], age (women: 46 years, men: 43.4 years)[8] and the mean standard serum creatinine concentration (women: 0.75 mg/dl, men: 0.9 mg/dl)[9] for women and men in Germany in 2021.

[7] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

[8] Federal Institute for Population Research, Average age of the population in Germany (1871-2021) https://www.bib.bund.de/DE/Fakten/Fakt/B19-Durchschnittsalter-Bevoelkerung-ab-1871.html

[9] DocCheck Flexikon – Serum creatinine, URL: https://flexikon.doccheck.com/de/Serumkreatinin [last access: 18.01.2024]

The mean value (AUC 4.5 = 630.7 mg) formed from these doses for women (AUC 4.5 = 573.3 mg) and men (AUC 4.5 = 688.1 mg) was used as the basis for calculating the cost of carboplatin.

Treatment period:

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

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 in combination with pembrolizumab				
Enfortumab vedotin	2 x per 21-day cycle	17.4	2	34.8
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
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	1 x per 28-day cycle	4.0 – 6.0	1	4 – 6
Gemcitabine	3 x per 28-day cycle	4.0 – 6.0	3	12 – 18
Maintenance treatment with avelumab				
Avelumab	1 x per 14-day cycle	14.1 – 18.1	1	14.1 – 18.1

b) Adults with unresectable or metastatic urothelial cancer who are ineligible for a cisplatin-based therapy; first-line treatment

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Enfortumab vedotin in combination with pembrolizumab				
Enfortumab vedotin	2 x per 21-day cycle	17.4	2	34.8
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
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 x per 21-day cycle	4.0 – 6.0	1	4 – 6
Gemcitabine	2 x per 21-day cycle	4.0 – 6.0	2	8 – 12
Maintenance treatment with avelumab				
Avelumab	1 x per 14-day cycle	17.1 – 20.1	1	17.1 – 20.1

Consumption:

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

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 in combination with pembrolizumab					
Enfortumab vedotin	1.25 mg/kg BW = 97.1 mg	97.1 mg	2 x 30 mg + 2 x 20 mg	34.8	69.6 x 30 mg + 69.6 x 20 mg
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg
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	70 mg/m^2 BSA = 133.7 mg	133.7 mg	1 x 100 mg + 1 x 50 mg	4 – 6	4 x 100 mg + 4 x 50 mg – 6 x 100 mg + 6 x 50 mg
Gemcitabine	1,000 mg/m^2 BSA = 1,910 mg	1,910 mg	2 x 1,000 mg	12 – 18	24 x 1,000 mg – 36 x 1,000 mg
Maintenance treatment with avelumab					
Avelumab	800 mg	800 mg	4 x 200 mg	14.1 – 18.1	56.4 x 200 mg – 72.4 x 200 mg

b) Adults with unresectable or metastatic urothelial cancer who are ineligible for a cisplatin-based therapy; first-line treatment

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 in combination with pembrolizumab					
Enfortumab vedotin	1.25 mg/kg BW = 97.1 mg	97.1 mg	2 x 30 mg + 2 x 20 mg	34.8	69.6 x 30 mg + 69.6 x 20 mg
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg
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)					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Carboplatin	4.5 x [GFR+25] mg = 630.7 mg	630.7 mg	1 x 600 mg + 1 x 50 mg	4 – 6	4 x 600 mg + 4 x 50 mg – 6 x 600 mg + 6 x 50 mg
Gemcitabine	1,000 mg/m² BSA = 1,910 mg	1,910 mg	1 x 2,000 mg	8 – 12	8 x 2,000 mg – 12 x 2,000 mg
Maintenance treatment with avelumab					
Avelumab	800 mg	800 mg	4 x 200 mg	17.1 – 20.1	68.4 x 200 mg – 80.4 x 200 mg

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 Sections 130 and 130 a 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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

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 30 mg	1 PCI	€ 833.35	€ 1.77	€ 45.51	€ 786.07
Enfortumab vedotin 20 mg	1 PCI	€ 559.32	€ 1.77	€ 30.34	€ 527.21
Pembrolizumab 100 mg	1 CIS	€ 2,743.07	€ 1.77	€ 153.37	€ 2,587.93
Appropriate comparator therapy					
a) Adults with unresectable or metastatic urothelial carcinoma who are eligible for a cisplatin-based therapy; first-line treatment					
Gemcitabine 1,000 mg	1 PIS	€ 102.35	€ 1.77	€ 10.62	€ 89.96
Cisplatin 50 mg	1 CIS	€ 47.71	€ 1.77	€ 1.73	€ 44.21
Cisplatin 100 mg	1 CIS	€ 76.59	€ 1.77	€ 3.10	€ 71.72
Avelumab 200 mg	1 CIS	€ 834.82	€ 1.77	€ 45.59	€ 787.46

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
b) Adults with unresectable or metastatic urothelial carcinoma who are ineligible for a cisplatin-based therapy; first-line treatment					
Carboplatin 600 mg	1 CIS	€ 300.84	€ 1.77	€ 13.74	€ 285.33
Carboplatin 50 mg	1 CIS	€ 34.66	€ 1.77	€ 1.11	€ 31.78
Gemcitabine 2,000 mg	1 CIS	€ 194.23	€ 1.77	€ 8.68	€ 183.78
Avelumab 200 mg	1 CIS	€ 834.82	€ 1.77	€ 45.59	€ 787.46
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 March 2025

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.

According to the avelumab product information, patients are required to be premedicated with an antihistamine and paracetamol prior to the first 4 infusions of avelumab. The product information does not provide any specific information why the necessary costs cannot be quantified.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of 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.

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

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	Costs/ patient/ year
Appropriate comparator therapy							
Cisplatin in combination with gemcitabine							
Cisplatin (4 to 6 cycles)							
Antiemetic treatment: In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified.							
Hydration and forced diuresis							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 105.54	€ 5.28	€ 4.26	€ 96.00	4 – 6	€ 96.00
Sodium chloride 0.9% inf. sol., 3 - 4.4 l/day	20 x 500 ml INF	€ 5.51	€ 0.28	€ 0.38	€ 4.85	4 – 6	€ 9.70 – 14.55

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 1 October 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 agents 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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 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

According to Section 35a, paragraph 3, sentence 4, the G-BA designates 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.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or

- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same

combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

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.

Justification for the findings on designation in the present resolution:

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

   Each of the designated medicinal products is an active ingredient that is specifically named as a concomitant active ingredient in the product information for the assessed medicinal product. Corresponding text extract from the product information for the assessed medicinal product: "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."

For the designated medicinal products, the requirements of Section 35a, paragraph 3, sentence 4 SGB V are also fulfilled.

References:
Product information for enfortumab vedotin (Padcev); Padcev 20 mg powder for solution for infusion; Padcev 30 mg powder for a concentrate for the preparation of a solution for infusion; last revised: 7 January 2025

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)

Supplement to Annex XIIa of the Pharmaceuticals Directive

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive and provided with patient-group-related information on the period of validity of the designation.

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 their session on 29 August 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. Working group 35a adapted the appropriate comparator therapy at their session on 13 August 2024.

On 20 September 2024 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 2 VerfO.

By letter dated 23 September 2024 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 20 December 2024, and the written statement procedure was initiated with publication on the G-BA website on 2 January 2025. The deadline for submitting statements was 23 January 2025.

The oral hearing was held on 10 February 2025.

By letter dated 11 February 2025, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 14 March 2025.

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 25 March 2025, and the proposed draft resolution was approved.

At their session on 3 April 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	29 August 2023	Determination of the appropriate comparator therapy
Working group Section 35a	13 August 2024	Implementation of the appropriate comparator therapy
Working group Section 35a	4 February 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	10 February 2025	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 February 2025 4 March 2025 18 March 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	25 March 2025	Concluding discussion of the draft resolution
Plenum	3 April 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 3 April 2025

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

Prof. Hecken