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) Durvalumab (new therapeutic indication: biliary tract cancer, first-line, combination with gemcitabine and cisplatin)

of 5 October 2023

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The active ingredient durvalumab (Imfinzi) was listed for the first time on 15 October 2018 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 7 November 2022, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for durvalumab, among others, in the therapeutic indication "Imfinzi in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic biliary tract cancer" in accordance with Section 35a paragraph 5b SGB V. The pharmaceutical company expected marketing authorisations for the active ingredient durvalumab within the period specified in Section 35a paragraph 5b SGB V for a total of three new therapeutic indications at different times. For two of the three new therapeutic indications, the pharmaceutical company expected marketing authorisation of durvalumab in combination with the active ingredient tremelimumab. The use of durvalumab in these two new

therapeutic indications thus requires not only the corresponding marketing authorisation decisions but also the first marketing of the medicinal product Imjudo with the active ingredient tremelimumab. For this reason, the date for the submission of a dossier for the benefit assessment of

- durvalumab in combination with tremelimumab in adults for first-line treatment of advanced or unresectable hepatocellular carcinoma (HCC) (therapeutic indication B); and
- durvalumab in combination with tremelimumab and platinum-based chemotherapy in adults for first-line treatment of metastatic NSCLC with no sensitising EGFR mutations or ALK-positive mutations (therapeutic indication C)

in these new therapeutic indications was determined to be the date of first placing on the market of the medicinal product Imjudo with the active ingredient tremelimumab. The pharmaceutical company expected the first marketing authorisation for the medicinal product Imjudo with the active ingredient tremelimumab in 2023 in the 1st quarter and planned the first placing on the market in Germany on 1 April 2023.

At its session on 15 December 2022, the G-BA approved the application pursuant to Section 35a paragraph 5b SGB V and postponed the relevant date for the start of the benefit assessment and the submission of a dossier for the benefit assessment for the therapeutic indication in question to the start of the assessment procedures for the new therapeutic indications B and C on the date of the first placing on the market of the necessary concomitant active ingredient Imjudo with the active ingredient tremelimumab, at the latest six months after the first relevant date.

For the therapeutic indication in question here "Imfinzi in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC)", durvalumab received the extension of the marketing authorisation as a major type 2 variation as defined according to Annex 2 No. 2 letter a to Regulation (EC) No. 1234/2008 of the Commission from 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, 12.12.2008, p. 7) on 16 December 2022. The marketing authorisation for Imjudo with the active ingredient tremelimumab in the therapeutic indications B and C was granted on 20 February 2023, and Imjudo was listed for the first time on 1 April 2023 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices. In accordance with the resolution of 15 December 2022, the benefit assessment for the active ingredient durvalumab in this new therapeutic indication thus began on 1 April 2023 at the latest.

On 29 March 2023, the pharmaceutical company has submitted in due time a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient durvalumab with the new therapeutic indication "Imfinzi in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC)".

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on the G-BA website (www.g-ba.de) on 3 July 2023, 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 durvalumab 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, and the

statements submitted in the written statement and oral hearing procedure, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 durvalumab.

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 Durvalumab (Imfinzi) in accordance with the product information

Imfinzi in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC)**.**

Therapeutic indication of the resolution (resolution of 05.10.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with unresectable or metastatic biliary tract cancer (BTC); first-line therapy

Appropriate comparator therapy for durvalumab in combination with gemcitabine and cisplatin:

- Cisplatin in combination with gemcitabine (cf. Annex VI to Section K of the Pharmaceuticals Directive)

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 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 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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. Besides durvalumab, no other medicinal products are currently approved in the therapeutic indication to be considered.

on 2. A non-medicinal treatment cannot be considered as an appropriate comparator therapy in this therapeutic indication.

on 3. In the therapeutic indication to be considered, there are no resolutions from the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications (off-label use, last revised: 24.06.2023): Cisplatin in combination with gemcitabine for advanced carcinomas of the gallbladder and bile ducts: systemic, medicinal first-line chemotherapy with cisplatin

plus gemcitabine in patients with locally advanced, unresectable, relapsed or metastatic carcinomas of the gallbladder and/or bile ducts.

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

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

Overall, the evidence for first-line treatment of unresectable or metastatic biliary tract cancer is limited. Besides durvalumab in combination with gemcitabine and cisplatin, no other medicinal products are currently approved.

However, the national S3 guideline and international guidelines clearly recommend a combination therapy consisting of cisplatin and gemcitabine.

For the therapy of unresectable or metastatic biliary carcinomas, the present written statement of the scientific-medical societies also comments that the standard in systemic first-line therapy is the combination of cisplatin and gemcitabine, which is supplemented by a symptom-oriented, supportive therapy.

The combination therapy of cisplatin and gemcitabine is not approved for the treatment of advanced carcinomas of the gallbladder and bile ducts, but can be prescribed as "off-label use" (cf. Annex VI to Section K of the Pharmaceuticals Directive).

Against the background of the therapy carried out in the intervention arm with durvalumab in combination with gemcitabine and cisplatin, it is assumed that the patients are eligible for intensive combination chemotherapy with regard to any comorbidity and the general condition.

Overall, the G-BA therefore determined cisplatin in combination with gemcitabine (cf. Appendix VI to Section K of the Pharmaceuticals Directive) as an appropriate comparator therapy.

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 durvalumab is assessed as follows:

Indication of a minor additional benefit

Justification:

For the proof of the additional benefit of durvalumab, the pharmaceutical company presented the results of the TOPAZ-1 study.

TOPAZ-1 is an ongoing, multicentre, double-blind, randomised controlled phase III study, comparing durvalumab in combination with gemcitabine and cisplatin to cisplatin in combination with gemcitabine. Adult patients with advanced, unresectable or metastatic biliary carcinoma were enrolled. These are unlikely to have previously received systemic therapy for advanced, unresectable or metastatic disease. Patients with prior curative chemotherapy or radiotherapy could be enrolled in the case of disease recurrence if the therapy had been completed at least 6 months prior to randomisation.

810 patients were enrolled in TOPAZ-1 and randomised in a 1:1 ratio to either treatment with durvalumab in combination with gemcitabine and cisplatin (N = 405) or treatment with cisplatin in combination with gemcitabine (N = 405). The number of randomised patients is based on 2 pooled cohorts. A global cohort of 685 patients (341 in the intervention arm, 344 in the control arm) and a China extension cohort of 125 patients (64 in the intervention arm, 61 in the control arm).

Randomisation was stratified according to disease status (initially unresectable vs recurrent disease) and primary tumour location (intrahepatic bile duct carcinoma vs extrahepatic bile duct carcinoma vs gallbladder carcinoma).

In both the intervention and control arms, cisplatin was administered in combination with gemcitabine in a 3-week cycle on days 1 and 8 for 8 cycles or for a maximum of 24 weeks. In the intervention arm, durvalumab was additionally given on day 1 of the cycle, while placebo was given in the control arm. After completion of chemotherapy, durvalumab or placebo was administered as monotherapy on day 1 in a 4-week cycle.

Treatment was given until disease progression (clinical or determined by RECIST criteria version 1.1), unacceptable toxicity, initiation of other tumour therapy, withdrawal of consent, or death. It was not possible to switch from the intervention arm to the control arm.

The currently ongoing study is being conducted at 121 study sites in Asia, Europe, North America and South America.

For the present benefit assessment, pooled analyses of the global cohort and the China extension cohort of the TOPAZ-1 study were submitted by the pharmaceutical company in the dossier based on different data cut-offs:

Data cut-off of the global cohort from 11.08.2021: This is the pre-specified interim analysis of overall survival. Since a statistically significant result for the endpoint of overall survival in favour of durvalumab was already shown at this point, this data cut-off also represents the final analysis.

Data cut-off of the global cohort from 25.02.2022: This is the analysis of the extended follow-up of overall survival and side effects at the time of the originally planned final analysis.

Data cut-off of the China extension cohort from 14.10.2022: This is the pre-specified data cut-off for evaluating overall survival for the same percentage of events in which a statistically significant difference was found in the global cohort.

Overall, the present benefit assessment is based on the pooled analyses of the two cohorts using the following data cut-offs:

- Endpoints in the overall survival and side effects:

    - global cohort: Data cut-off from 25.02.2022
    - China expansion cohort: Data cut-off from 14.10.2022
- Endpoints of the category of morbidity and health-related quality of life
    - global cohort: Data cut-off from 11.08.2021
    - China expansion cohort: Data cut-off from 14.10.2022

The primary endpoint of the TOPAZ-1 study was overall survival. Patient-relevant secondary endpoints include endpoints in the categories of morbidity, health-related quality of life and side effects.

Extent and probability of the additional benefit

Mortality

For the endpoint of overall survival, there is a statistically significant difference to the advantage of durvalumab in combination with gemcitabine and cisplatin compared to cisplatin in combination with gemcitabine.

Although the prolongation of survival time achieved is assessed as a relevant improvement, its extent is minimal.

Morbidity

Progression-free survival (PFS)

PFS was operationalised in the TOPAZ-1 study as the time from randomisation to the first RECIST 1.1-defined radiological disease progression or death from any cause without prior progression, regardless of whether the patient discontinued therapy or received other antineoplastic therapy prior to progression.

There is a statistically significant difference to the advantage of durvalumab in combination with gemcitabine and cisplatin compared to cisplatin in combination with gemcitabine.

The PFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component "mortality" was already assessed as an independent endpoint in the present study via the endpoint "overall survival". The morbidity component assessment was not done in a symptom-related manner but exclusively by means of imaging (disease progression assessed by radiology according to the RECIST 1.1 criteria).

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 extent of the additional benefit remains unaffected.

Symptomatology (assessed using EORTC QLQ-C30, EORTC QLQ-BIL21 and PGIS)

The symptomatology of the patients is assessed in the study with the EORTC QLQ-C30 and the disease-specific additional module EORTC QLQ-BIL21 as well as the PGIS.

EORTC QLQ-C30, EORTC QLQ-BIL21

For the benefit assessment, the pharmaceutical company submitted evaluations of the time to first deterioration by at least 10 points. These are used as basis for the present assessment.

In the disease-specific additional module EORTC QLQ-BIL21, for the endpoint of drainage difficulties, there is a statistically significant difference to the disadvantage of durvalumab in combination with gemcitabine and cisplatin compared to cisplatin in combination with gemcitabine.

PGIS (Patient's Global Impression of Severity)

The PGIS is a patient-reported 1-item measurement tool to assess the severity of symptoms or symptom complexes on a scale from 0 (no symptoms) to 6 (very severe symptoms). Higher values are associated with more severe symptomatology of the patients.

For the benefit assessment, the pharmaceutical company submitted evaluations of the first deterioration to 5 points (severe symptoms) or 6 points (very severe symptoms). These are used as basis for the present assessment.

For PGIS, there is no statistically significant difference between the treatment groups.

Health status (assessed by EQ-5D VAS)

The health status is assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. Evaluations of the time to first deterioration by at least 15 points were submitted by the pharmaceutical company and used as a basis for the present assessment.

For the endpoint of health status, there is no statistically significant difference between the treatment groups.

In the overall analysis of the results on symptomatology as well as the health status, no relevant difference for the benefit assessment between the treatment groups was found.

Quality of life

The quality of life of patients is assessed in the TOPAZ-1 study using functional scales of the EORTC QLQ-C30 questionnaire and the disease-specific additional module EORTC QLQ-BIL21.

For the benefit assessment, evaluations of the time to first deterioration by at least 10 points were submitted by the pharmaceutical company and used as a basis for the present assessment.

There was no statistically significant difference between the treatment groups for any of the scales of the health-related quality of life.

In the overall analysis of the results, there is neither an advantage nor a disadvantage of durvalumab in combination with gemcitabine and cisplatin with regard to health-related quality of life.

Side effects

Adverse events in total

Adverse events occurred in almost all patients. The results for the endpoint "total adverse events" are only presented additionally.

Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3), therapy discontinuation due to AEs

There were no statistically significant differences between the treatment arms for the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs.

Specific AEs

Immune-mediated SAEs, immune-mediated severe AEs (CTCAE ≥ 3)

In the dossier for the benefit assessment, the pharmaceutical company did not submit any evaluations of the immune-mediated AEs. Therefore, evaluations of immune-mediated SAEs and immune-mediated severe AEs based on the AEs of special interest (AESI) pre-specified in the TOPAZ-1 study were used for the benefit assessment. However, for the AESI in the pooled cohort, only results which, contrary to the predefinition, additionally included the standardised MedDRA queries (SMQs) diseases of the liver, biliary diseases and haematopoietic cytopenias, were available in the dossier. These SMQs partly represent symptoms of the underlying disease and side effects of chemotherapy. Further analyses of the AESI without inclusion of the above-mentioned SMQs for the pooled cohort were submitted by the pharmaceutical company as part of the written statement procedure. These will be used for the present assessment.

For the immune-mediated SAEs and immune-mediated severe AEs (CTCAE grade ≥ 3), there is no statistically significant difference between the treatment groups.

Skin and subcutaneous tissue disorders (SAEs), fever (SAEs), anaemia (SAEs) and cholangitis (severe SAEs)

For the specific AEs of skin and subcutaneous tissue disorders (AE), fever (SAE), anaemia (SAE) and cholangitis (severe AE), there is a statistically significant difference to the disadvantage of durvalumab in combination with gemcitabine and cisplatin compared to cisplatin in combination with gemcitabine.

In the overall assessment of the results on side effects, there is neither an advantage nor a disadvantage of durvalumab in combination with gemcitabine and cisplatin. In detail, there are disadvantages in the specific AEs.

Overall assessment

For the assessment of the additional benefit of durvalumab in combination with gemcitabine and cisplatin, results are available from the TOPAZ-1 study for comparison with cisplatin in combination with gemcitabine for the endpoint categories of mortality, morbidity, quality of life and side effects.

For overall survival, there is a statistically significant difference to the advantage of durvalumab in combination with gemcitabine and cisplatin compared to cisplatin in combination with gemcitabine. Although the prolongation of survival time achieved is assessed as a relevant improvement, its extent is minimal.

For symptomatology (assessed using the EORTC QLQ-C30, EORTC QLQ-BIL21 and PGIS) as well as for health status (assessed using EQ-5D VAS), no relevant difference for the benefit assessment is found between the treatment groups overall.

With regard to the endpoint categories of health-related quality of life (assessed using EORTC QLQ-C30 and EORTC QLQ-BIL21) and side effects, there are neither advantages nor disadvantages of durvalumab in combination with gemcitabine and cisplatin. In detail, there are disadvantages in the specific AEs for side effects.

In the overall analysis of the present results on the patient-relevant endpoints, the advantage in overall survival is not offset by any assessment relevant disadvantages in other endpoint categories.

As a result, durvalumab in combination with gemcitabine and cisplatin for first-line therapy of adults with unresectable or metastatic biliary tract cancer (BTC) is found to have a minor additional benefit compared to cisplatin in combination with gemcitabine.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the multicentre, randomised, controlled, double-blind TOPAZ-1 study.

At the study level, the risk of bias is considered low.

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

For the other endpoint categories of morbidity, quality of life and side effects, the respective endpoint-specific risk of bias is also estimated to be low.

In the overall assessment, the reliability of data for the additional benefit determined 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 durvalumab.

The therapeutic indication assessed here is as follows:

"Imfinzi in combination with gemcitabine and cisplatinn is indicated for the first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC)."

The G-BA determined cisplatin in combination with gemcitabine (cf. Annex VI to Section K of the Pharmaceuticals Directive) as the appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company submits the still ongoing, double-blind phase III TOPAZ-1 study for the comparison of durvalumab in combination with gemcitabine and cisplatin versus gemcitabine in combination with cisplatin.

For overall survival, there is an advantage for patients in the intervention arm. Although the prolongation of survival time achieved is assessed as a relevant improvement, its extent is minimal.

For symptomatology and health status, no relevant difference for the benefit assessment between the treatment groups was found.

With regard to the endpoint categories of health-related quality of life and side effects, there are neither advantages nor disadvantages of durvalumab in combination with gemcitabine and cisplatin. In detail, there are disadvantages in the specific AEs for side effects.

Based on the advantage in overall survival, the overall assessment shows an indication of a minor additional benefit of durvalumab in combination with gemcitabine and cisplatin compared to cisplatin in combination with gemcitabine.

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 resolution is based on the information from the dossier of the pharmaceutical company. These patient numbers are underestimated.

The main reasons for this are the limitation to UICC tumour stage IV and the exclusion of patients with several differently localised biliary carcinomas.

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 Imfinzi (active ingredient: durvalumab) at the following publicly accessible link (last access: 20 September 2023):

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

Treatment with durvalumab should only be initiated and monitored by specialists in internal medicine, haematology and oncology as well as specialists in internal medicine and gastroenterology and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with biliary tract cancer.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 September 2023).

The costs for the first year of treatment are shown for the cost representation in the resolution.

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration 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.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed:				
Durvalumab in combination with gemcitabine and cisplatin				
Durvalumab	Cycle 1 – 8: Day 1 of a 21-day cycle From cycle 9 onwards: Day 1 of a 28-day cycle	1st year 15.0	1	1st year 15.0
Gemcitabine	Cycle 1 – 8: Day 1 and 8 of a 21-day cycle	8.0	2	16.0
Cisplatin	Cycle 1 – 8: Day 1 and 8 of a 21-day cycle	8.0	2	16.0
Appropriate comparator therapy				
Cisplatin in combination with gemcitabine (cf. Annex VI to Section K of the Pharmaceuticals Directive)				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Cisplatin	Cycle 1 – 8: Day 1 and 8 of a 21-day cycle	8.0	2	16.0
Gemcitabine	Cycle 1 – 8: Day 1 and 8 of a 21-day cycle	8.0	2	16.0

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments, e.g. because of side effects or comorbidities, 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 2017 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916).[2]

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					
Durvalumab in combination with gemcitabine and cisplatin					
Durvalumab	1,500 mg	1,500 mg	3 x 500 mg	15.0	45.0 x 500 mg
Cisplatin	25 mg/m² BSA = 47.5 mg	47.5 mg	1 x 50 mg	16.0	16.0 x 50 mg
Gemcitabine	1,000 mg/m² BSA = 1,900 mg	1,900 mg	1 x 2,000 mg	16.0	16.0 x 2,000 mg
Appropriate comparator therapy					
Cisplatin in combination with gemcitabine (cf. Annex VI to Section K of the Pharmaceuticals Directive)					
Cisplatin	25 mg/m² BSA = 47.5 mg	47.5 mg	1 x 50 mg	16.0	16.0 x 50 mg

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Gemcitabine	1,000 mg/m² BSA = 1,900 mg	1,900 mg	1 x 2,000 mg	16.0	16.0 x 2,000 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 Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Durvalumab 500 mg	1 CIS	€ 2,167.38	€ 2.00	€ 206.55	€ 1,958.83
Cisplatin 50 mg	1 CIS	€ 47.73	€ 2.00	€ 4.61	€ 41.12
Gemcitabine 2,000 mg	1 CIS	€ 194.23	€ 2.00	€ 8.68	€ 183.55
Appropriate comparator therapy					
Cisplatin 50 mg	1 CIS	€ 47.73	€ 2.00	€ 4.61	€ 41.12
Gemcitabine 2,000 mg	1 CIS	€ 194.23	€ 2.00	€ 8.68	€ 183.55
Abbreviations: CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 15 September 2023

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.

Because there are no 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, no costs for

additionally required SHI services need to be taken into account.

Other SHI services:

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

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (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.

In the case of information on "determined" or "undetermined" combinations, the assessed medicinal product can be used in a combination therapy according to this information on the basis of the marketing authorisation under Medicinal Products Act. For the designation, the G-BA, within the scope of its legislative discretion, uses the constellation of a "determined" or an "undetermined" combination as a justifiable interpretation variant.

If a designation as a so-called determined or as a so-called indetermined combination is omitted due to the lack of information on a combination therapy in the product information of the assessed medicinal product, the non-designation in the resolution according to Section 35a, paragraph 3, sentence 1 SGB V does not affect the possibility that the assessed medicinal product can be used in an open-label combination under marketing authorisation regulations.

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 information 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 SGBV.

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:

Adults with unresectable or metastatic biliary tract cancer (BTC); first-line therapy

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 9 March 2022, 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. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 24 January 2023.

By resolution of 15 December 2022, the G-BA postponed the relevant date for the start of the benefit assessment and the submission of a dossier for the benefit assessment for the therapeutic indication in question here to the start of the assessment procedures for two further new therapeutic indications for durvalumab (therapeutic indication B: durvalumab in combination with tremelimumab in adults for first-line treatment of advanced or unresectable heptocellular carcinoma (HCC) as well as therapeutic indication C: durvalumab in combination with tremelimumab and platinum-based chemotherapy in adults for first-line treatment of metastatic NSCLC with no sensitising EGFR mutations or ALK-positive mutations) to the date of the first placing on the market of the concomitant active ingredient with the active ingredient tremelimumab, which is required for use post-authorisation in the therapeutic indications in question according to Section 35a paragraph 5b SGB V. The medicinal product Imjudo with the active ingredient tremelimumab was first placed on the market on 1 April 2023.

On 29 March 2023, the pharmaceutical company submitted a dossier for the benefit assessment of durvalumab to the G-BA in due time.

By letter dated 30 March 2023 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 durvalumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 June 2023, and the written statement procedure was initiated with publication on the G-BA website on 3 July 2023. The deadline for submitting statements was 24 July 2023.

The oral hearing was held on 7 August 2023.

By letter dated 9 August 2023, 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 15 September 2023.

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 26 September 2023, and the proposed resolution was approved.

At its session on 5 October 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	9 March 2022	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	24 January 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	2 August 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 August 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	6 September 2023 20 September 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	26 September 2023	Concluding discussion of the draft resolution
Plenum	5 October 2023	Adoption of the resolution on the amendment of the AM-RL

Berlin, 5 October 2023

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

Prof. Hecken