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 Durvalumab (new therapeutic indication: primary advanced or recurrent endometrial cancer, combination with carboplatin and paclitaxel; maintenance treatment, combination with olaparib)

of 20 February 2025

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 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 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 26 July 2024, durvalumab 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, 12.12.2008, sentence 7).

On 21 August 2024, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 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 durvalumab with the new therapeutic indication

"IMFINZI in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with IMFINZI in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR)."

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The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 December 2024 on the G-BA website at (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 durvalumab compared to 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. 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 carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with IMFINZI in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR).

Therapeutic indication of the resolution (resolution of 20.02.2025):

See the approved therapeutic indication

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with primary advanced endometrial carcinoma (Stage III or IV) or recurrent endometrial carcinoma with mismatch repair proficiency (pMMR) who:

- have not yet received systemic therapy as postoperative or adjuvant therapy for treatment of the primary advanced disease,
- have not yet received chemotherapy for treatment of the recurrence.

Appropriate comparator therapy:

- Carboplatin + paclitaxel followed by monitoring wait-and-see approach

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.

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

on 1. .In addition to durvalumab, medicinal products with the active ingredients cisplatin, doxorubicin, medroxyprogesterone acetate, megestrol acetate, pembrolizumab and dostarlimab are approved in this therapeutic indication. The active ingredient olaparib is approved for maintenance treatment.

on 2. Non-medicinal treatment is not considered.

on 3. No corresponding resolutions or assessments of the G-BA are available.

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

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

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

In view of the fact that the approved therapeutic indication clearly covers different treatment settings, this is specified as follows when determining the appropriate comparator therapy:

Adult patients with primary advanced endometrial carcinoma (Stage III or IV) or recurrent endometrial carcinoma with mismatch repair proficiency (pMMR) who:

- have not yet received systemic therapy as postoperative or adjuvant therapy for treatment of the primary advanced disease,
- have not yet received chemotherapy for treatment of the recurrence.

For determination of the appropriate comparator therapy, it is assumed that local therapy options for treating the recurrence (resection, radiotherapy) are not an option for patients in the therapeutic indication in the recurrence situation.

The current S3 guideline[2] does not include a recommendation that takes the pMMR status into account for patients in this therapeutic indication. There are recommendations that are independent of the pMMR status and are therefore suitable for an unselected patient population in this regard. Systemic chemotherapy can be carried out in accordance with the recommendations of this treatment setting. The S3 guideline recommends chemotherapy with carboplatin in combination with paclitaxel as the evidence-based treatment of choice.

As part of the written statement procedure, clinical experts stated that the determined appropriate comparator therapy (combination of carboplatin and paclitaxel) corresponds to the recommendations of the scientific-medical societies.

The active ingredients pembrolizumab and dostarlimab (each in combination with carboplatin and paclitaxel) are new treatment options in this therapeutic indication. The active ingredients were only recently approved for this therapeutic indication (marketing authorisation of pembrolizumab on 21.10.2024; marketing authorisation of dostarlimab on 15.01.2025). Based on the generally accepted state of medical knowledge, pembrolizumab and dostarlimab are not determined to be an appropriate comparator therapy for the present resolution.

The active ingredients carboplatin and paclitaxel are not approved for the present treatment setting, neither as individual active ingredients nor in the combination of carboplatin and paclitaxel. Accordingly, the use of carboplatin in combination with paclitaxel represents an off-label use. Due to the evidence-based recommendation of the use of chemotherapy with carboplatin in combination with paclitaxel in the S3 guideline, the off-label use of these active ingredients according to the generally recognised state of medical knowledge in the therapeutic indication to be assessed is therefore currently considered the therapy standard in the medical treatment situation as it would be without the medicinal product to be assessed.

As the resolutions of the G-BA on the benefit assessment in accordance with Section 35a SGBV for the approved active ingredients pembrolizumab and dostarlimab in the therapeutic indications to be assessed are still pending, there is currently a lack of a sound basis for decision-making in order to be able to carry out a structured, evidence-based assessment of the newly approved active ingredients also in relation to the active ingredients that form the therapy standard in the therapeutic indication. Against this background, these active ingredients could not yet be taken into account with regard to the determination of the therapy standard in the therapeutic indication to be assessed in accordance with Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV).

According to the generally recognised state of medical knowledge, the off-label use of carboplatin in combination with paclitaxel must generally be preferred over the medicinal products previously approved in the therapeutic indication, Section 6, paragraph 2, sentence 3, number 2 AM-NutzenV.

Therefore, it is appropriate to determine the off-label use of carboplatin in combination with paclitaxel as the appropriate comparator therapy.

[2] Guideline program in oncology (German Cancer Society, German Cancer Aid, Association of the Scientific-Medical Societies). Endometrial carcinoma; S3 guideline, long version 3.0. AWMF registry number 032-034OL. Berlin (GER): Oncology guideline programme; 2024.

For maintenance treatment following first-line therapy, the S3 guideline currently includes no recommendations for an active therapy of patients with pMMR endometrial cancer.

In view of the fact that the present therapeutic indication provides for maintenance treatment, "monitoring wait-and-see approach" is considered to be a suitable comparison for this phase of the treatment sequence.

Overall, the G-BA therefore determined carboplatin in combination with paclitaxel followed by monitoring wait-and-see approach as the 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:

Adult patients with primary advanced endometrial carcinoma (Stage III or IV) or recurrent endometrial carcinoma with mismatch repair proficiency (pMMR) who:

- have not yet received systemic therapy as postoperative or adjuvant therapy for treatment of the primary advanced disease,
- have not yet received chemotherapy for treatment of the recurrence.

a) Patients with newly diagnosed disease:

Indication of a considerable additional benefit

b) Patients with recurrent disease:

An additional benefit is not proven.

Justification:

For the benefit assessment, the pharmaceutical company presented the results of the ongoing, triple-arm, randomised, double-blind phase III DUO-E study. The study is being conducted in 202 study sites across Australia, Asia, Europe and America.

The DUO-E study comprises 3 study arms:

- Placebo + carboplatin + paclitaxel, followed by placebo (arm A),
- Durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab + placebo (arm B),
- Durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab + olaparib (arm C).

Adult patients with histologically confirmed diagnosis of epithelial endometrial cancer of any histology (including carcinosarcoma) and regardless of their mismatch repair (MMR) status

were enrolled in the study. In addition to patients with newly diagnosed International Federation of Gynaecology and Obstetrics (FIGO) stage III or FIGO stage IV disease, patients with recurrence whose chances of recovery through surgery alone or in combination with radiotherapy or systemic therapy are low were also enrolled. The patients must not have received any systemic therapy for the current stage of the disease. Only for patients with recurrent disease was prior systemic treatment permitted, provided it was administered as part of adjuvant treatment (as part of preparatory or adjuvant cancer treatment, which could be administered concomitantly or following chemoradiotherapy) and at least 12 months had elapsed between the last dose of systemic treatment and the time of the subsequent recurrence.

A total of 718 patients with endometrial cancer were enrolled in the study and randomised in a ratio of 1:1:1 to one of the 3 treatment arms (arm A, N = 241; arm B, N = 238; arm C, N = 239). Stratification was based on (deficient vs proficient) MMR status, disease status (newly diagnosed vs recurrent) and geographical region (Asia vs rest of the world).

The DUO-E study is divided into 2 phases. In the 1st phase (initial therapy), all patients received carboplatin and paclitaxel in combination with durvalumab or placebo for a minimum of 4 to a maximum of 6 cycles. Patients who showed no signs of radiological disease progression subsequently received maintenance treatment with durvalumab and placebo (arm B), durvalumab and olaparib (arm C) or placebo (arm A), depending on the treatment arm. Patients with pMMR status from arm A and arm C are used for the assessment.

The placebo comparison conducted in maintenance treatment in arm A of the DUO-E study adequately corresponds to the implementation of the monitoring wait-and-see approach in the appropriate comparator therapy.

The primary endpoint of the DUO-E study was progression-free survival (PFS). Secondary endpoints were overall survival and endpoints in the categories of morbidity, health-related quality of life and side effects.

3 data cut-offs are available for the ongoing DUO-E study:

- Data cut-off from 30.06.2022: Futility analysis on the PFS for the global population
- Data cut-off from 12.04.2023: Primary analysis of the PFS for the global population
- Data cut-off from 18.10.2023: 120-day safety update for the Food and Drug Administration (FDA).

The pharmaceutical company presented the pre-specified data cut-off from 12.04.2023 for the endpoints in the endpoint categories of mortality, morbidity, health-related quality of life and side effects, as well as analyses for the endpoints in the categories of mortality and side effects for the data cut-off from 18.10.2023. The available information does not indicate that the FDA explicitly requested the data cut-off from 18.10.2023. The pre-specified data cut-off from 12.04.2023 is used for the benefit assessment.

Extent and probability of the additional benefit

Analysis across endpoints

In the subgroup analyses on the characteristic "disease status at baseline (newly diagnosed vs recurrent)", there was an effect modification for each of the endpoints of overall survival and symptomatology (nausea and vomiting assessed using EORTC QLQ-C30). In this respect, a statistically significant advantage in overall survival was only observed in patients with newly diagnosed disease. In terms of symptomatology, a statistically significant disadvantage was only observed in patients with recurrent disease.

As part of the written statement procedure, the clinical experts discussed this difference in effect against the background of the small sample size and the underlying biology of the corresponding disease stages and considered a separate analysis of these stages meaningless.

Due to the effect modification, the G-BA considers it appropriate in the present case to make a separate statement on the additional benefit depending on the characteristic "disease status at baseline" in the overall assessment. In the present assessment, the group of patients with newly diagnosed disease and the group of patients with recurrent disease are assessed separately. This approach is considered appropriate, taking into account the percentage of subgroups in the total study population, the extent of effect differences between the subgroups and the clinically relevant demarcation between newly diagnosed disease and recurrent disease. In the DUO-E study, the disease status at baseline (newly diagnosed vs recurrent) was a stratification factor.

Mortality

Overall survival in the DUO-E study was operationalised as the time from randomisation to death from any cause.

For the endpoint of overall survival, there was a statistically significant difference in the total population to the advantage of durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab and olaparib compared to placebo in combination with carboplatin and paclitaxel, followed by placebo.

For this endpoint, there was an effect modification by the "disease status at baseline" characteristic. In this regard, the subgroup of patients with newly diagnosed disease showed a statistically significant advantage of durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab and olaparib. The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

In the subgroup of patients with recurrent disease, there was no statistically significant difference between the treatment arms, which is why no advantage can be derived here.

Morbidity

Progression-free survival

Progression-free survival (PFS) was operationalised in the DUO-E study as the time from randomisation to first objective disease progression or death from any cause. The endpoint was collected by principal investigators on site and was assessed according to the RECIST criteria version 1.1.

For the PFS endpoint, there was a statistically significant advantage of durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab and olaparib compared to the appropriate comparator therapy.

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 version 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 additional benefit remains unaffected.

Symptomatology

Symptomatology was assessed using the EORTC QLQ-C30, EORTC QLQ-EN24 and Patient Global Impression of Severity (PGIS) instruments. The evaluations of time to first deterioration are used for the benefit assessment.

EORTC QLQ-C30 and EORTC QLQ-EN24

For the endpoints collected using EORTC QLQ-C30 and EORTC QLQ-EN24, the evaluations of time to first deterioration by ≥ 10 points are used.

There was no statistically significant difference between the treatment groups for each of the endpoints of fatigue, pain, insomnia and diarrhoea (assessed using EORTC QLQ-C30) and the endpoints of lymphoedema, urological symptoms, gastrointestinal symptoms, back and pelvic pain, tingling/ numbness, muscular pain and hair loss (assessed using EORTC QLQ-EN24).

For the endpoints of dyspnoea, appetite loss and constipation (assessed using EORTC QLQ-C30) and for the endpoint of change in taste (assessed using EORTC QLQ-EN24), there was a statistically significant difference to the disadvantage of durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab + olaparib.

For the endpoint of nausea and vomiting (assessed using EORTC QLQ-C30), there was a statistically significant difference to the disadvantage of durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab + olaparib. For this endpoint, there was an effect modification by the "disease status at baseline" characteristic. In this respect, there was no difference between the treatment groups in the subgroup of patients with newly diagnosed disease. In the subgroup of patients with recurrent disease, there was a statistically significant disadvantage of durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab and olaparib compared with the appropriate comparator therapy.

No suitable data are available for the endpoint of sexual/ vaginal problems (assessed using EORTC QLQ-EN24), as a maximum of 29 vs 25 patients (15% vs 13%) had a baseline value and a further value in the course of the study.

Patient Global Impression of Severity (PGIS)

For the PGIS, the pharmaceutical company submitted post hoc time-to-event analyses on the 1st deterioration, where they define deterioration as an increase by ≥ 1 point compared to the start of the study. An increase by ≥ 1 point compared to the start of the study is considered deterioration that is quite certain to reflect a noticeable change in the patients. The time-to-event analyses on the first deterioration submitted by the pharmaceutical company are used.

For symptomatology assessed using PGIS, there was no statistically significant difference between the treatment groups.

Health status (EQ-5D VAS and PGIC)

Health status was assessed using the EQ-5D VAS and PGIC instruments. The evaluations of time to first deterioration are used for the benefit assessment.

For health status assessed using EQ-5D VAS, there was no statistically significant difference between the treatment groups.

For the PGIC, the pharmaceutical company submitted post hoc time-to-event analyses on the first deterioration in the dossier, where they only define the responses "moderately worse" or "much worse" as an event. Patients who rate their health status as "minimally worse" compared to the start of the study medication are therefore not included in the evaluation. However, a slight deterioration also represents a patient-relevant change. The time-to-event analyses on the first deterioration submitted by the pharmaceutical company are therefore unsuitable for the benefit assessment.

Quality of life

EORTC QLQ-C30 and EORTC QLQ-EN24

Health-related quality of life was assessed using the EORTC QLQ-C30 and EORTC QLQ-EN24 instruments. The evaluations on the time to first deterioration by ≥ 10 points is used for the benefit assessment.

There was no statistically significant difference between the treatment groups for each of the endpoints of global health status, physical functioning, role functioning, emotional functioning and social functioning (assessed using EORTC QLQ-C30) and for the endpoints of libido, sexual activity and negative body image (assessed using EORTC QLQ-EN24).

For the endpoint of cognitive functioning (assessed using EORTC QLQ-C30), there was no statistically significant difference between the treatment groups.

No suitable data are available for the endpoint of sexual pleasure (assessed using EORTC QLQ-EN24), as a maximum of 29 vs 25 patients (15% vs 13%) had a baseline value and a further value in the course of the study.

Side effects

Adverse events (AEs) in total

In the DUO-E study, AEs occurred in both study arms in almost all patients. The results were only presented additionally.

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

There was no statistically significant difference between the treatment groups for the endpoints of SAEs and discontinuation due to AEs.

Specific AEs

Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

The pharmaceutical company did not provide any information on PRO-CTCAE in the dossier. In the study protocol, the selection process of the PRO-CTCAE items is not transparent and the selection of the items for mapping the symptomatic AEs of durvalumab, carboplatin, paclitaxel and olaparib is incomprehensible. For this reason, the results of the PRO-CTCAE cannot be used for the benefit assessment.

Immune-mediated SAEs and immune-mediated severe AEs

The data on immune-mediated AEs presented by the pharmaceutical company are based on a combination of the adverse events of special interest (AESI) for durvalumab and the AESI for olaparib collected in the study (including new primary malignancy, MDS/ AML) as well as adverse events of possible interest (AEPI) for durvalumab, for which an inflammatory or immune-mediated response is less likely as a potential cause and/or which are mostly or usually due to other causes. Overall, the analyses presented by the pharmaceutical company are unsuitable for the depiction of immune-mediated AEs.

No suitable data are therefore available for the PRO-CTCAE and the endpoints of immune-mediated SAEs and immune-mediated severe AEs.

Myelodysplastic syndrome (MDS)/ acute myeloid leukaemia (AML) (SAEs)

For the endpoint of MDS/ AML (SAEs), no events occurred in either treatment arm and there was no statistically significant difference between the treatment groups.

Pneumonitis (severe AEs)

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

Anaemia (severe AEs)

For the endpoint of anaemia (severe AEs), there was a statistically significant difference to the disadvantage of durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab and olaparib compared to placebo in combination with carboplatin and paclitaxel, followed by placebo.

Overall assessment

Results on mortality, morbidity, health-related quality of life and side effects from the 3-arm, randomised, double-blind DUO-E study are available for the assessment of the additional benefit of durvalumab in combination with carboplatin and paclitaxel, followed by maintenance treatment with durvalumab in combination with olaparib in the treatment of patients with mismatch repair proficient (pMMR) primary advanced endometrial cancer (stage III or IV) or recurrent endometrial cancer.

In the subgroup analyses on the characteristic "disease status at baseline (newly diagnosed vs recurrent)", there was an effect modification for each of the endpoints of overall survival and symptomatology (nausea and vomiting assessed using EORTC QLQ-C30). Due to the described effect modification, the group of patients with newly diagnosed disease and the group of patients with recurrent disease are considered separately in the overall assessment.

a) Patients with newly diagnosed disease:

For the endpoint of overall survival, there was a statistically significant difference to the advantage of durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab and olaparib. The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

With regard to symptomatology, the endpoints of dyspnoea, appetite loss and constipation (each assessed using EORTC QLQ-C30) and change in taste (assessed using EORTC QLQ-EN24) showed a statistically significant disadvantage of durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab and olaparib. There was no relevant difference between the treatment groups for the endpoint of nausea and vomiting (assessed using EORTC QLQ-C30), symptomatology assessed using PGIS and health status (assessed using EQ-5D VAS). In the overall assessment of all endpoints on symptomatology and health status, a moderate disadvantage in the morbidity endpoint category was observed overall.

For health-related quality of life, there were no statistically significant differences between the treatment groups.

In terms of side effects, durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab and olaparib, showed no disadvantages for the endpoints of severe AEs, serious AEs and therapy discontinuation due to AEs, but a statistically significant disadvantage for the specific AE of anaemia.

In the overall analysis, the clear advantage in overall survival is offset by moderate disadvantages for the endpoints in the morbidity endpoint category. These disadvantages do not question the extent of the improvement in overall survival. No relevant difference for the benefit assessment was found for the endpoint categories of health-related quality of life and side effects.

As a result, a considerable additional benefit of durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab and olaparib, was identified in the group of patients with newly diagnosed disease.

b) Patients with recurrent disease:

For the endpoint of overall survival, there was no difference between the treatment arms.

With regard to symptomatology, the endpoints of dyspnoea, nausea and vomiting, appetite loss and constipation (each assessed using EORTC QLQ-C30) and change in taste (assessed using EORTC QLQ-EN24) showed a statistically significant disadvantage of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib. There was no relevant difference between the treatment groups for symptomatology assessed using PGIS and health status (assessed by EQ-5D VAS). In the overall assessment of all endpoints on symptomatology and health status, a moderate disadvantage in the morbidity endpoint category was observed overall.

For health-related quality of life, there were no statistically significant differences between the treatment groups.

In terms of side effects, durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab and olaparib, showed no disadvantages for the endpoints of severe AEs, serious AEs and therapy discontinuation due to AEs, but a statistically significant disadvantage for the specific AE of anaemia.

Overall, there was no relevant difference for the benefit assessment in the endpoint categories of overall survival, health-related quality of life and side effects. There are moderate disadvantages with regard to morbidity.

As a result, no additional benefit of durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab and olaparib was identified for patients with recurrent disease.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the 3-arm, randomised, double-blind DUO-E study. The risk of bias at study level is rated as low.

The risk of bias of the results for the endpoint of overall survival and for side effects is rated as low.

For the patient-reported endpoints on symptomatology, health status and health-related quality of life, there was no baseline value or no value in the course of the study for a relevant percentage of patients. This results in a high risk of bias of all effect estimates on patient-reported data.

Overall, an indication is derived for the reliability of data of the additional benefit identified.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient durvalumab.

"IMFINZI in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with IMFINZI in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR)."

The combination of carboplatin and paclitaxel followed by the monitoring wait-and-see approach was determined as the appropriate comparator therapy.

In the subgroup analyses on the characteristic "disease status at baseline (newly diagnosed vs recurrent)", there was an effect modification for each of the endpoints of overall survival and symptomatology (nausea and vomiting assessed using EORTC QLQ-C30). Due to the described effect modification, the group of patients with newly diagnosed disease and the group of patients with recurrent disease are considered separately in the overall assessment.

Adult patients with primary advanced endometrial carcinoma (Stage III or IV) or recurrent endometrial carcinoma with mismatch repair proficiency (pMMR) who:

- have not yet received systemic therapy as postoperative or adjuvant therapy for treatment of the primary advanced disease,
- have not yet received chemotherapy for treatment of the recurrence.

a) Patients with newly diagnosed disease

b) Patients with recurrent disease:

On a)

For the endpoint of overall survival, there was a statistically significant advantage of durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib compared to carboplatin in combination with paclitaxel, followed by the monitoring wait-and-see approach. The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

With regard to symptomatology, the endpoints of dyspnoea, appetite loss, constipation and change in taste showed a statistically significant disadvantage of durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab and olaparib.

There were no statistically significant differences for health-related quality of life and side effects.

In the overall analysis, the clear advantage in overall survival is offset by moderate disadvantages for the endpoints in the morbidity endpoint category. These disadvantages do not question the extent of the improvement in overall survival.

As a result, a considerable additional benefit of durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab and olaparib, was identified in the group of patients with newly diagnosed disease.

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

On b)

For the endpoint of overall survival, there was no statistically significant difference between the treatment arms.

With regard to symptomatology, the endpoints of dyspnoea, nausea and vomiting, appetite loss, constipation and change in taste showed a statistically significant disadvantage for durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib.

There were no statistically significant differences for health-related quality of life and side effects.

In conclusion, the G-BA identified no additional benefit for durvalumab + carboplatin + paclitaxel, followed by durvalumab + olaparib compared with carboplatin in combination with paclitaxel, followed by the monitoring wait-and-see approach for patients with recurrent disease in a summarised interpretation of the data.

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 patient numbers from the dossier of the pharmaceutical company. The information on the number of patients in the SHI target population are largely mathematically plausible, but for methodological reasons are associated with uncertainties overall, which result primarily from the following aspects:

The information provided by the pharmaceutical company was based on an incidence that does not only include endometrial cancer. In addition, the distribution of FIGO stages was not adequately determined and it is unclear to what extent the populations, on which the percentage values for recurrence are based, are representative. It is also questionable whether the percentage of doctors who favour a chemotherapy regimen is the same as the percentage of patients for whom this treatment is an option.

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: 5 November 2024):

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, specialists in gynaecology, and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with endometrial cancer.

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: 1 February 2025).

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.

There are no approved medicinal products for the therapy options defined as appropriate comparator therapy in the present therapeutic indication. The cost representation of the individual therapy options is based on the respective referenced sources.

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 of women: 1.66 m, average body weight of women: 69.2 kg). This results in a body surface area of 1.77 m² (calculated according to Du Bois 1916)[3].

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

The dosage according to the target AUC of carboplatin is calculated using the Calvert formula and the estimation of renal function with the Cockcroft-Gault equation using the average height (average body height of women: 1.66 m)[3], the average weight (average body weight of women: 69.2 kg)[3], the average age of women in Germany in 2021 (46 years)**Fehler! Textmarke nicht definiert.** and the average standard serum creatinine concentration (women: 0.75 mg/dl)[4].

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

Treatment period:

Adult patients with primary advanced endometrial carcinoma (Stage III or IV) or recurrent endometrial carcinoma with mismatch repair proficiency (pMMR) who:

- have not yet received systemic therapy as postoperative or adjuvant therapy for treatment of the primary advanced disease,
- have not yet received chemotherapy for treatment of the recurrence.

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 carboplatin and paclitaxel				
Durvalumab	1 x every 21 days	4 – 6	1	4 – 6
Carboplatin	1 x every 21 days	4 – 6	1	4 – 6
Paclitaxel	1 x every 21 days	4 – 6	1	4 – 6
Maintenance treatment with durvalumab in combination with olaparib				
Durvalumab	1 x every 28 days	8.5 – 10.0	1	8.5 – 10.0
Olaparib	Continuously, 2 x daily	239.0 – 281.0	1	239.0 – 281.0
Appropriate comparator therapy				
Carboplatin + paclitaxel[5]				
Carboplatin	1 x every 21 days	17.4	1	17.4
Paclitaxel	1 x every 21 days	17.4	1	17.4

Consumption:

Adult patients with primary advanced endometrial carcinoma (Stage III or IV) or recurrent endometrial carcinoma with mismatch repair proficiency (pMMR) who:

[4] DocCheck Flexikon – Serum creatinine, URL: https://flexikon.doccheck.com/de/Serumkreatinin [last access: 25.04.2024]

[5] S3 guideline endometrial cancer, long version 2.0 – September 2022, AWMF registry number: 032/034-OL

- have not yet received systemic therapy as postoperative or adjuvant therapy for treatment of the primary advanced disease,
- have not yet received chemotherapy for treatment of the recurrence.

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 carboplatin and paclitaxel					
Durvalumab	1,120 mg	1,120 mg	2 x 500 mg + 1 x 120 mg	4 – 6	8 x 500 mg+ 4 x 120 mg – 12 x 500 mg + 6 x 120 mg
Carboplatin	AUC 5 = 637 mg or AUC 6 = 764.3 mg	637 mg – 764.3 mg	1 x 600 mg + 1 x 50 mg – 1 x 600 mg + 1 x 150 mg + 1 x 50 mg	4 – 6	4 x 600 mg + 4 x 50 mg – 6 x 600 mg + 6 x 150 mg + 6 x 50 mg
Paclitaxel	175 mg/m^2 BSA = 309.8 mg	309.8 mg	1 x 300 mg + 1 x 30 mg	4 – 6	4 x 300 mg + 4 x 30 mg – 6 x 300 mg + 6 x 30 mg
Maintenance treatment with durvalumab in combination with olaparib					
Durvalumab	1,500 mg	1,500 mg	3 x 500 mg	8.5 – 10.0	25.5 x 500 mg – 30 x 500 mg
Olaparib	2 x daily 300 mg	600 mg	4 x 150 mg	239.0 – 281.0	956 x 150 mg – 1,124 x 150 mg
Appropriate comparator therapy					
Carboplatin + paclitaxel[5]					
Carboplatin	AUC 6 = 764.3 mg	764.3 mg	1 x 600 mg + 1 x 150 mg + 1 x 50 mg	17.4	17.4 x 600 mg + 17.4 x 150 mg + 17.4 x 50 mg
Paclitaxel	175 mg/m^2 BSA = 309.8 mg	309.8 mg	1 x 300 mg + 1 x 30 mg	17.4	17.4 x 300 mg + 17.4 x 30 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:

Adult patients with primary advanced endometrial carcinoma (Stage III or IV) or recurrent endometrial carcinoma with mismatch repair proficiency (pMMR) who:

- have not yet received systemic therapy as postoperative or adjuvant therapy for treatment of the primary advanced disease,
- have not yet received chemotherapy for treatment of the recurrence.

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 120 mg	1 CIS	€ 518.21	€ 1.77	€ 28.06	€ 488.38
Durvalumab 500 mg	1 CIS	€ 2,105.19	€ 1.77	€ 116.94	€ 1,986.48
Carboplatin 600 mg	1 CIS	€ 300.84	€ 1.77	€ 13.74	€ 285.33
Carboplatin 150 mg	1 CIS	€ 83.06	€ 1.77	€ 3.40	€ 77.89
Carboplatin 50 mg	1 CIS	€ 34.66	€ 1.77	€ 1.11	€ 31.78
Paclitaxel 300 mg	1 CIS	€ 845.77	€ 1.77	€ 39.60	€ 804.40
Paclitaxel 30 mg	1 CIS	€ 94.76	€ 1.77	€ 3.96	€ 89.03
Olaparib 150 mg	112 FCT	€ 4,763.36	€ 1.77	€ 268.74	€ 4,492.85
Appropriate comparator therapy					
Carboplatin 600 mg	1 CIS	€ 300.84	€ 1.77	€ 13.74	€ 285.33
Carboplatin 150 mg	1 CIS	€ 83.06	€ 1.77	€ 3.40	€ 77.89
Carboplatin 50 mg	1 CIS	€ 34.66	€ 1.77	€ 1.11	€ 31.78
Paclitaxel 300 mg	1 CIS	€ 845.77	€ 1.77	€ 39.60	€ 804.40
Paclitaxel 30 mg	1 CIS	€ 94.76	€ 1.77	€ 3.96	€ 89.03
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 February 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.

As the appropriate comparator therapy in the present case was exceptionally determined as the off-label use of medicinal products, no statement can be made as to whether there are regular differences in the necessary use of medical treatment or in the prescription of other services when using the medicinal product to be assessed compared with the appropriate comparator therapy according to the product information. Therefore, no costs for additionally required SHI services are taken into account here.

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 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.

Adult patients with primary advanced endometrial carcinoma (Stage III or IV) or recurrent endometrial carcinoma with mismatch repair proficiency (pMMR) who:

- have not yet received systemic therapy as postoperative or adjuvant therapy for treatment of the primary advanced disease,
- have not yet received chemotherapy for treatment of the recurrence.

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:

"IMFINZI in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with IMFINZI in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR)".

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

References:
Product information for durvalumab (Imfinzi); Imfinzi 50 mg/ml concentrate for the preparation of an infusion solution; last revised: 18.12.2024

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 its session on 10 October 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. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 6 August 2024.

On 21 August 2024 the pharmaceutical company submitted a dossier for the benefit assessment of durvalumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 22 August 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 durvalumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 November 2024, and the written statement procedure was initiated with publication on the G-BA website on 2 December 2024. The deadline for submitting statements was 23 December 2024.

The oral hearing was held on 6 January 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 11 February 2025, and the proposed draft resolution was approved.

At its session on 20 February 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	10 October 2023	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	6 August 2024	New determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	6 January 2025	Information on statements received, conduct of the oral hearing
Working group Section 35a	14 January 2025 4 February 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	11 February 2025	Concluding discussion of the draft resolution
Plenum	20 February 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 20 February 2025

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

Prof. Hecken