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)
Dostarlimab (new therapeutic indication: dMMR/ MSI-H primary advanced or recurrent endometrial cancer, combination with carboplatin and paclitaxel)

of 20 June 2024

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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 dostarlimab (Jemperli) was listed for the first time on 15 June 2021 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 7 December 2023, dostarlimab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334 from 12.12.2008, sentence 7).

On 19 December 2023, the pharmaceutical company has submitted a dossier in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication) in accordance with Section 4, paragraph 3, No.2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with

Chapter 5 Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient dostarlimab with the new therapeutic indication:

"JEMPERLI is indicated in combination with carboplatin and paclitaxel for the treatment of adult patients with mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy."

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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 April 2024 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of dostarlimab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of dostarlimab.

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 Dostarlimab (Jemperli) in accordance with the product information

JEMPERLI is indicated in combination with carboplatin and paclitaxel for the treatment of adult patients with mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy.

Therapeutic indication of the resolution (resolution of 20 June 2024):

"see approved therapeutic indication”

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Adult patients with primary advanced endometrial cancer (stage III or IV) or with recurrence of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) endometrial cancer 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 for dostarlimab in combination with carboplatin and paclitaxel followed by treatment with dostarlimab as monotherapy:

Carboplatin + paclitaxel

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. Based on the authorisation status, the active ingredients cisplatin, doxorubicin, medroxyprogesterone acetate and megestrol acetate are available for treatment in the present therapeutic indication.

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 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”). There is a joint written statement from the German Society for Haematology and Medical Oncology (DGHO) and the North-East German Society for Gynaecological Oncology (NOGGO).

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 microsatellite instability-high (MSI-H) or with mismatch repair deficient (dMMR) primary advanced endometrial cancer (stage III or IV) or with recurrence of endometrial cancer 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.

Furthermore, when determining the appropriate comparator therapy, it was assumed that in the recurrence situation, local therapy options for treating the recurrence (resection, radiotherapy) are not an option for patients in the therapeutic indication.

According to the present state of knowledge, there are no specific therapy recommendations for the specified therapeutic indication, depending on the MSI-H/dMMR status.

Furthermore, the available evidence does not indicate that certain factors are present in MSI-H/dMMR tumours in the therapeutic indication that clearly speak against

treatment with the previous or current standard therapies. Thus, those therapy options that are independent of the MSI/dMMR status and thus, eligible for the unselected patient population in this respect are considered for the appropriate comparator therapy.

According to the recommendations of the S3 guideline on endometrial cancer[2], systemic chemotherapy can be carried out in the present treatment setting. The active ingredients cisplatin and doxorubicin are approved for this purpose. However, the S3 guideline recommends chemotherapy with carboplatin in combination with paclitaxel as the evidence-based treatment of choice.

This is consistent with the written statement of the scientific-medical societies that the therapy standard in first-line treatment of primary advanced or recurrent endometrial cancer is combination chemotherapy with carboplatin and paclitaxel.

The active ingredients carboplatin and paclitaxel are not approved for the present indication.

Accordingly, the use of carboplatin in combination with paclitaxel represents an off-label use. For patients in the named therapeutic indication, the off-label use according to the generally recognised state of medical knowledge is generally preferable to 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 medicinal products 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 dostarlimab in combination with carboplatin and paclitaxel is assessed as follows:

a) Adult patients with microsatellite instability-high (MSI-H) or with mismatch repair deficient (dMMR) primary advanced endometrial cancer (stage III or IV) or with recurrence of endometrial cancer 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.

a1) Patients with primary advanced disease

An additional benefit is not proven.

[2] Guideline program in oncology (German Cancer Society, German Cancer Aid, Association of the Scientific Medical Societies). Endometrial carcinoma; S3 guideline, long version, version 2.0. AWMF registry number 032-034OL. Berlin (GER): Oncology guideline programme; 2022.

a2) Patients with recurrent disease

Indication of a major additional benefit.

Justification:

To demonstrate an additional benefit of dostarlimab in combination with carboplatin and paclitaxel for the treatment of adult patients with primary advanced endometrial cancer (stage III or IV) or with recurrence of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) endometrial cancer, the pharmaceutical company presents in the dossier the results at the 1st data cut-off (pre-specified interim analysis) from 28 September 2022 of the ongoing RUBY study, which has been conducted in 108 study sites, particularly in Europe and North America, since August 2019. As part of the written statement procedure, the pharmaceutical company submitted evaluations for the RUBY study at a pre-specified 2nd data cut-off (22.09.2023).

The RUBY study is a two-part randomised, controlled, double-blind phase III study in which part 1, which is relevant for the benefit assessment, compares dostarlimab in combination with carboplatin and paclitaxel to carboplatin in combination with paclitaxel.

A total of 494 adult patients with primary advanced *(International Federation of Gynaecology and Obstetrics* [FIGO] stage III or IV) or recurrent endometrial cancer, whose disease had a low chance of cure by radiotherapy and/or surgery alone or in combination and who were in good general condition, according to an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 or 1, were enrolled in the study. Randomisation was performed in a 1:1 ratio to treatment with dostarlimab in combination with carboplatin and paclitaxel (N = 245) or carboplatin in combination with paclitaxel (N = 249), stratified by mismatch repair/ microsatellite stability status (dMMR/ MSI-H vs mismatch repair proficiency/ microsatellite stability), disease stage at the start of study (primary FIGO stage III vs primary FIGO stage IV vs recurrent) and prior external pelvic radiotherapy (yes vs no). Treatment in the intervention arm was carried out in accordance with the product information. The combination of carboplatin and paclitaxel used in the control arm, which is not approved in this therapeutic indication but is considered standard in the first-line therapy of primary advanced or recurrent endometrial cancer according to national and international guidelines, was used in accordance with the dosage recommended in the guidelines.

Relevant sub-population of the RUBY study

In the dossier, the pharmaceutical company presented data on the benefit assessment-relevant sub-population of patients with dMMR/MSI-H endometrial cancer, corresponding to the therapeutic indication according to the product information. With 53 patients in the treatment arm and 65 patients in the control arm, this comprised a total of 118 patients with dMMR/MSI-H advanced or recurrent endometrial cancer.

The primary endpoint of the study is progression-free survival (PFS) in the relevant sub-population with dMMR/MSI-H status. Patient-relevant secondary endpoints were assessed in the categories of mortality, morbidity, health-related quality of life and side effects.

Extent and probability of the additional benefit

Analysis across endpoints

In the subgroup analyses on the characteristic "disease status at baseline" (primary FIGO III vs primary FIGO IV vs. recurrent), there was a consistent effect modification in two data cut-offs for each of the endpoints of overall survival, symptomatology ("tingling/numbness" assessed using the EORTC QLQ-EN24) and severe adverse events. A statistically significant advantage in overall survival was only observed in the most recent data cut-off (27.09.2023) in patients with recurrent disease. In terms of symptomatology, a statistically significant advantage is only observed in patients in FIGO stage IV and in terms of serious adverse events, a statistically significant disadvantage is only observed in patients in FIGO stage III.

During 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, which is consistently shown in two data cut-offs, 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 "primary advanced disease" (FIGO stage III/ FIGO stage IV) and the group of patients with "recurrent disease" are assessed separately. Thus, for the group of patients with "primary advanced disease", the data from the subgroup analyses on the characteristics "FIGO stage III" and "FIGO stage IV" are interpreted accordingly for a summary statement. 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 "primary advanced disease" and "recurrent disease".

Mortality

Overall survival

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

For this endpoint, there was a statistically significant difference in favour of dostarlimab in combination with carboplatin and paclitaxel compared to carboplatin in combination with paclitaxel in the total population.

Both data cut-offs presented by the pharmaceutical company consistently show an effect modification according to "disease status at baseline". The most recent data cut-off (27.09.2023) showed a statistically significant advantage in favour of dostarlimab in combination with carboplatin and paclitaxel only for patients with recurrent disease at baseline. In this regard, the extent of the prolongation achieved in overall survival is assessed as a very significant improvement.

For patients in FIGO stages III and IV, the subgroup analyses showed no difference between the treatment arms, so that no advantage can be derived from an overall interpretation of the data.

Morbidity

Progression-free survival

Progression-free survival in the RUBY study was defined as the time between randomisation and the earliest documented disease progression or death from any cause without prior progression, based on the time of first radiological documentation of disease progression according to the RECIST - (*Response Evaluation Criteria In Solid Tumours*, version 1.1) criteria version 1.1. PFS as assessed by a principal investigator was a primary efficacy endpoint in the study, while PFS as assessed by a blinded independent central review (BICR) was a secondary endpoint.

Dostarlimab in combination with carboplatin and paclitaxel statistically significantly prolongs the rPFS compared to carboplatin in combination with paclitaxel. The present rPFS is a composite endpoint consisting of endpoints from the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component "disease progression" is collected according to RECIST criteria and thus predominantly by means of imaging procedures.

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

The overall statement on the additional benefit remains unaffected.

Cross-endpoint assessment of patient-reported endpoints (PRO) data:

For the benefit assessment, the pharmaceutical company submits a main analysis for the "time to first clinically relevant deterioration/ improvement" and a supplementary analysis for the "time to permanent clinically relevant deterioration/ improvement" for each of the endpoints in the categories of morbidity and health-related quality of life collected in the RUBY study using the EORTC QLQ-C30 and EORTC QLQ-EN24 questionnaires and the EQ-5D visual analogue scale.

For improvement/ deterioration

In the present therapeutic indication, a progressive course of the disease is to be expected, which means that the time to deterioration is considered a more suitable operationalisation in this case.

On first/ permanent change

In the operationalisation presented by the pharmaceutical company, both the time to first change and the time to permanent change are fundamentally patient-relevant.

However, in particular due to a different number of surveys and a differential decrease in the percentage of completed questionnaires between the treatment arms, the evaluation of the permanent change is unusable in this case.

Consequently, the time to first deterioration is used, especially since this is not affected to a relevant extent by the different survey intervals or number of surveys.

Symptomatology (EORTC QLQ-C30 and EORTC QLQ-EN24)

Symptomatology was surveyed using the EORTC QLQ-C30 questionnaire and its disease-specific supplementary module EORTC QLQ-EN24. The time to first deterioration of ≥ 10 points is used for the benefit assessment.

In the total population, there was no statistically significant difference between the treatment arms for the endpoint of time to first deterioration of symptomatology, surveyed using the EORTC QLQ-C30 and EORTC QLQ-EN24 questionnaires.

However, there is an advantage in the symptom scale "tingling/numbness" of the EORTC QLQ-EN24 in patients with primary advanced disease exclusively in FIGO stage IV. For patients with primary advanced disease in FIGO stage III, the subgroup analysis showed no difference between the treatment arms. No advantage can be derived from the overall interpretation of the data.

Health status (EQ-5D VAS)

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. The time to first deterioration of ≥ 15 points is used for the benefit assessment.

There was no statistically significant difference between the treatment arms in the total population for the endpoint of time to first deterioration in health status, surveyed with the EQ-5D VAS.

In the overall analysis of the results on morbidity, there were no relevant differences for the benefit assessment.

Quality of life

EORTC QLQ-C30 and EORTC QLQ-EN24

Health-related quality of life was surveyed using the EORTC QLQ-C30 questionnaire and its disease-specific supplementary module EORTC QLQ-EN24. The time to first deterioration of ≥ 10 points is used for the benefit assessment.

For the endpoint "time to first deterioration in health-related quality of life", surveyed using the EORTC QLQ-C30 and EORTC QLQ-EN24, the functional scales "role functioning" and "social functioning" showed a statistically significant advantage in favour of dostarlimab in combination with carboplatin and paclitaxel over carboplatin in combination with paclitaxel. This advantage is independent of the "disease status at baseline" in the total population.

There was no statistically significant difference between the treatment arms in the other functional scales.

In the overall analysis of the results on health-related quality of life, there was a moderate advantage in favour of dostarlimab in combination with carboplatin and paclitaxel, both in patients with primary advanced disease and in patients with recurrent disease.

Side effects

Adverse events in total

In the RUBY study, AEs occurred in all patients in both treatment arms. The results were only presented additionally.

Serious AEs (SAEs), severe AEs and discontinuation due to AEs

For the endpoints of SAEs, severe AEs and discontinuation due to AEs, there were no statistically significant differences between the treatment arms in the total population.

In patients with primary advanced disease in FIGO stage III, however, there was a statistically significant disadvantage of dostarlimab in combination with carboplatin and paclitaxel for the

endpoint of severe AEs. For patients in FIGO stage IV, the subgroup analysis showed no difference between the treatment arms. In the overall interpretation of the data, no disadvantage can be derived for patients with primary advanced disease.

Specific AEs

In detail, the specific adverse events in the total population showed a statistically significant difference to the advantage of dostarlimab in combination with carboplatin and paclitaxel over carboplatin in combination with paclitaxel with regard to urinary tract infections. With regard to immune-mediated severe AEs, 12 (23%) events occurred in the intervention arm and none in the control arm in the total population.

In the overall analysis of the results, neither an advantage nor a disadvantage was found on the whole for treatment with dostarlimab in combination with carboplatin and paclitaxel compared to carboplatin in combination with paclitaxel with regard to the results on side effects.

Overall assessment

For the assessment of the additional benefit of dostarlimab in combination with carboplatin and paclitaxel in patients with primary advanced endometrial cancer (stage III or IV) or with recurrence of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) endometrial cancer, results on mortality, morbidity, health-related quality of life and side effects from the randomised, double-blind, multicentre, controlled RUBY study are available. In the RUBY study, dostarlimab in combination with carboplatin and paclitaxel was compared with carboplatin in combination with paclitaxel. The assessment is based on the 2nd data cut-off of the RUBY study from 22 September 2023.

In the subgroup analyses on the characteristic "disease status at baseline" (primary FIGO III vs primary FIGO IV vs. recurrent), there was an effect modification for each of the endpoints of overall survival, symptomatology ("tingling/numbness" assessed using the EORTC QLQ-EN24) and severe adverse events.

Due to the described effect modification, the group of patients with "primary advanced disease" (FIGO stage III/FIGO stage IV) and the group of patients with "recurrent disease" are assessed separately in the present assessment, so that the data from the subgroup analyses on the characteristics "FIGO stage III" and "FIGO stage IV" are interpreted accordingly for a summary statement for the group of patients with "primary advanced disease".

a1) Patients with primary advanced disease

In patients with primary advanced disease, overall interpretation of the data shows no difference between the treatment groups in the overall survival endpoint category.

In the morbidity endpoint category, patients with primary advanced disease in FIGO stage IV showed a statistically significant advantage in favour of dostarlimab in combination with carboplatin and paclitaxel in the endpoint of time to first deterioration in the symptom scale "tingling/numbness" of the EORTC QLQ-EN24. In the overall assessment, the overall interpretation of the data does not reveal any relevant differences for the benefit assessment.

For the endpoint category "health-related quality of life", treatment with dostarlimab in combination with carboplatin and paclitaxel showed a moderate advantage when analysing the "role functioning" and "social functioning" functional scales of the EORTC QLQ-C30.

For the endpoint category of side effects, dostarlimab in combination with carboplatin and paclitaxel showed a disadvantage in patients with primary advanced disease in FIGO stage III for severe AEs; there were no differences in the endpoints of serious AEs and therapy discontinuations due to AEs. There were no differences for patients in FIGO stage IV. In the overall assessment, no advantage or disadvantage relevant for the benefit assessment can be identified in the endpoint category "side effects" in the overall interpretation of the data.

In the overall assessment, there is only a moderate advantage in health-related quality of life, which is offset by a disadvantage in severe AEs with limited significance of the subgroup analysis for this endpoint. Considering the results for all other patient-relevant endpoints, neither an advantage nor a disadvantage of dostarlimab in combination with carboplatin and paclitaxel can be identified. An additional benefit is therefore not proven.

a2) Patients with recurrent disease

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

In the morbidity endpoint category, there were no statistically significant differences in the endpoints of time to first deterioration in symptomatology (surveyed using the EORTC QLQ-C30 and EORTC QLQ-EN24) and health status (surveyed using the EQ-5D VAS).

For the endpoint category "health-related quality of life", treatment with dostarlimab in combination with carboplatin and paclitaxel showed a moderate advantage when analysing the "role functioning" and "social functioning" functional scales of the EORTC QLQ-C30.

For the endpoint category of side effects, neither an advantage nor a disadvantage of dostarlimab in combination with carboplatin and paclitaxel compared to carboplatin in combination with paclitaxel could be identified in the overall analysis.

Overall, a major additional benefit of dostarlimab in combination with carboplatin and paclitaxel compared to carboplatin in combination with paclitaxel was identified.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the randomised, double-blind, multicentre controlled RUBY study. The risk of bias at the study level is rated as low.

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

At the endpoint level of the endpoint category of health-related quality of life, the risk of bias is rated as high in view of the sharp decline in return rates to the questionnaires, which differed between the treatment arms.

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 dostarlimab:

"JEMPERLI is indicated in combination with carboplatin and paclitaxel for the treatment of adult patients with mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy."

The combination of carboplatin and paclitaxel was determined as the appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company submitted data from the RUBY study. In part 1 of this two-part randomised, controlled, double-blind phase III study, patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer were randomised in a 1:1 ratio to the treatment arm (dostarlimab in combination with carboplatin and paclitaxel) and the control arm (carboplatin in combination with paclitaxel). The assessment is based on the pre-specified 2nd data cut-off of the RUBY study from 22 September 2023.

There was a consistent effect modification across two data cut-offs by the characteristic "disease status at baseline". There was an advantage in overall survival only for patients with recurrent disease.

Against this background, the G-BA considered a separate assessment of the additional benefit for patients with primary advanced disease and patients with recurrent disease to be appropriate, whereby in the present assessment for the group of patients with "primary advanced disease", the data from the subgroup analyses on the characteristics "FIGO stage III" and "FIGO stage IV" are interpreted accordingly for a summary statement:

a) Adult patients with microsatellite instability-high (MSI-H) or with mismatch repair deficient (dMMR) primary advanced endometrial cancer (stage III or IV) or with recurrence of endometrial cancer 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.

   a1) Patients with primary advanced disease

   a2) Patients with recurrent disease

On a1)

In the endpoint categories of mortality, morbidity and side effects, there were no relevant differences for the benefit assessment.

In the results on health-related quality of life, there were only moderate advantages of dostarlimab in combination with carboplatin compared to carboplatin in combination with paclitaxel.

As a result, the G-BA concluded in an overall interpretation of the data that an additional benefit of dostarlimab in combination with carboplatin and paclitaxel compared with carboplatin and paclitaxel for patients with primary advanced disease (FIGO stage III and FIGO stage IV) is not proven.

On a2)

For the overall survival endpoint, there is a very clear advantage of dostarlimab in combination with carboplatin compared to carboplatin in combination with paclitaxel.

In the endpoint category of health-related quality of life, there were moderate advantages of dostarlimab in combination with carboplatin compared to carboplatin in combination with paclitaxel.

There were no relevant differences for the benefit assessment in the endpoint categories of morbidity and side effects.

As a result, the G-BA identified a major additional benefit of dostarlimab in combination with carboplatin and paclitaxel compared with carboplatin and paclitaxel.

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

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

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

The G-BA bases its resolution on the information provided by IQWiG, as the information provided by the pharmaceutical company is methodologically overestimated.

The main reason for this is that the target population in the present treatment setting is assumed to be predominantly incident patients, but the pharmaceutical company uses the 5-year prevalence as the starting point for its calculation.

Further reasons are deviations between the observation period to which the percentage values refer and the duration of the disease of the patients in the 5-year prevalence as well as uncertain percentage values for patients with primary advanced or recurrent endometrial cancer due to unclear representativeness of the associated populations.

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 Jemperli (active ingredient: dostarlimab) at the following publicly accessible link (last access: 11 June 2024):

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

Treatment with dostarlimab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in obstetrics and gynaecology, and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with endometrial cancer.

All doctors prescribing Jemperli must inform patients about the patient card and explain what to do in case of symptoms of immune-mediated side effects. The doctor provides each patient with a patient card.

The dMMR/MSI-H tumour status should be determined using a validated investigation method.

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: 1 June 2024).

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.

The cost representation for dostarlimab in combination with carboplatin and paclitaxel is based on the treatment regimen used in the RUBY approval study. The respective dosage is based on the requirements in the product information.

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].

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)[4] and the average standard serum creatinine concentration (women: 0.75 mg/dl)[5].

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

Treatment period:

Adult patients with microsatellite instability-high (MSI-H) or with mismatch repair deficient (dMMR) primary advanced endometrial cancer (stage III or IV) or with recurrence of endometrial cancer 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				
Dostarlimab	1st – 6th cycle	1st – 6th cycle	1	1st – 6th cycle

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

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

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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	1 x every 21 days From 6th cycle 1 x every 42 days	6 From 6th cycle 5.7		6 From 6th cycle 5.7
Carboplatin	1 x every 21 days	6	1	6
Paclitaxel	1 x every 21 days	6	1	6
Appropriate comparator therapy				
Carboplatin + paclitaxel[6]				
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 microsatellite instability-high (MSI-H) or with mismatch repair deficient (dMMR) primary advanced endometrial cancer (stage III or IV) or with recurrence of endometrial cancer 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	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					
Dostarlimab + carboplatin + paclitaxel					
Dostarlimab	1st – 6th cycle 500 mg From 6th cycle 1,000 mg	1st – 6th cycle 500 mg From 6th cycle 1,000 mg	1st – 6th cycle 1 x 500 mg From 6th cycle 2 x 500 mg	1st – 6th cycle 6 From 6th cycle 5.7	6 x 500 mg + 11.4 x 500 mg
Carboplatin	AUC 5 = 637 mg	637 mg	1 x 600 mg + 1 x 50 mg	6	6 x 600 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	6	6 x 300 mg + 6 x 30 mg

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Carboplatin + paclitaxel[6]					
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 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. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Adult patients with microsatellite instability-high (MSI-H) or with mismatch repair deficient (dMMR) primary advanced endometrial cancer (stage III or IV) or with recurrence of endometrial cancer 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					
Dostarlimab 500 mg	1 CIS	€ 2,956.31	€ 2.00	€ 165.54	€ 2,788.77
Carboplatin 600 mg	1 CIS	€ 300.84	€ 2.00	€ 13.74	€ 285.10
Carboplatin 50 mg	1 CIS	€ 34.66	€ 2.00	€ 1.11	€ 31.55
Paclitaxel 300 mg	1 CIS	€ 845.77	€ 2.00	€ 39.60	€ 804.17
Paclitaxel 30 mg	1 CIS	€ 94.76	€ 2.00	€ 3.96	€ 88.80
Appropriate comparator therapy					

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
Paclitaxel 300 mg	1 CIS	€ 845.77	€ 2.00	€ 39.60	€ 804.17
Paclitaxel 30 mg	1 CIS	€ 94.76	€ 2.00	€ 3.96	€ 88.80
Carboplatin 600 mg	1 CIS	€ 300.84	€ 2.00	€ 13.74	€ 285.10
Carboplatin 150 mg	1 CIS	€ 83.06	€ 2.00	€ 3.40	€ 77.66
Carboplatin 50 mg	1 CIS	€ 34.66	€ 2.00	€ 1.11	€ 31.55
Abbreviations: CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 June 2024

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 1.10.2009 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 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 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.

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 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adult patients with microsatellite instability-high (MSI-H) or with mismatch repair deficient (dMMR) primary advanced endometrial cancer (stage III or IV) or with recurrence of endometrial cancer 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.

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.

Product information for dostarlimab (Jemperli); JEMPERLI 500 mg concentrate for the preparation of an infusion solution; last revised: June 2024

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 15 November 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 27 February 2024.

On 19 December 2023, the pharmaceutical company submitted a dossier for the benefit assessment of dostarlimab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 21 December 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 dostarlimab.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 March 2024, and the written statement procedure was initiated with publication on the G-BA website on 2 April 2024. The deadline for submitting statements was 23 April 2024.

The oral hearing was held on 6 May 2024.

By letter dated 7 May 2024, 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 30 May 2024.

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 June 2024, and the proposed resolution was approved.

At its session on 20 June 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	15 November 2023	Implementation of the appropriate comparator therapy
Subcommittee Medicinal products	27 February 2024	New implementation of the appropriate comparator therapy
Working group Section 35a	30 April 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	6 May 2024	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	15 May 2024 5 June 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	11 June 2024	Concluding discussion of the draft resolution
Plenum	20 June 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 20 June 2024

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

Prof. Hecken