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 Olaparib (Reassessment after the deadline: ovarian, fallopian tube or primary peritoneal cancer; maintenance treatment after first-line therapy; HRD-positive; combination with bevacizumab)

of 20 April 2023

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The pharmaceutical company submitted a dossier for the early benefit assessment of the active ingredient olaparib (Lynparza) on 30 November 2020. For the resolution of 3 June 2021 made by the G-BA in this procedure, a limitation up to 1 October 2022 was pronounced. At the pharmaceutical company's request, this limitation was extended until 1 December 2022 by the resolution of the G-BA of 16 June 2022. At the renewed request of the pharmaceutical company, the original limitation of the resolution of 1 December 2022 was shortened. For this purpose, advancing the deadline to 1 November 2022 was considered to be appropriate.

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Lynparza recommences when the deadline has expired.

The pharmaceutical company submitted . the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO on 28 October 2022. The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 February 2023 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 olaparib compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. 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 olaparib.

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 Olaparib (Lynparza) in accordance with the product information

Lynparza in combination with bevacizumab is indicated for the:

maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability.

Therapeutic indication of the resolution (resolution of 20.04.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

> Adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency

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

(HRD) positive status (defined by either a BRCA1/2-mutation and/or genomic instability); maintenance therapy

Appropriate comparator therapy for Olaparib in combination with bevacizumab:

- Continuation of treatment with bevacizumab started with platinum treatment as part of first-line chemotherapy regimen.

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

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

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

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

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

on 1. In addition to olaparib in combination with bevacizumab, medicinal products with the following active ingredients are approved for the maintenance treatment of advanced ovarian cancer after platinum-based first-line chemotherapy:

Bevacizumab, carboplatin, cisplatin, cyclophosphamide, doxorubicin, epirubicin, niraparib, olaparib, paclitaxel, treosulfan and melphalan.

on 2. No non-medicinal treatments can be considered.

on 3. The following resolutions and guidelines of the G-BA on medicinal treatments for the maintenance treatment of advanced ovarian cancer after platinum-based first-line chemotherapy are available:

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

- Olaparib: Resolution of 16 January 2020
- Niraparib: Resolution of 20 May 2021

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

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

According to current guidelines, chemotherapy with carboplatin in combination with paclitaxel is recommended as first-line therapy for advanced ovarian cancer.

Platinum-based first-line chemotherapy should be followed by additional maintenance treatment of advanced ovarian cancer.

According to the present therapeutic indication forming the basis of the resolution, olaparib in combination with bevacizumab is used as maintenance treatment in patients with a response (complete or partial) after platinum treatment as part of first-line chemotherapy regimen in combination with bevacizumab.

Based on platinum-based first-line chemotherapy in combination with the active ingredient bevacizumab, the available evidence suggests that bevacizumab or the combination of a PARP inhibitor with bevacizumab can be considered for maintenance treatment.

Maintenance treatment with bevacizumab is indicated if the primary therapy also included the use of bevacizumab. According to the bevacizumab product information, in this case, bevacizumab monotherapy is used following bevacizumab-containing primary treatment.

In addition, according to the current S3 guideline, bevacizumab in combination with a PARP inhibitor is recommended as maintenance treatment for patients who have a response (complete or partial) after completed platinum treatment within a first-line chemotherapy regimen in combination with bevacizumab and whose tumour is associated with positive homologous recombination deficiency (HRD) status defined by either a BRCA1/2 mutation or/and genomic instability.

In this regard, only data for the active ingredient olaparib are available so far. This is the combination of active ingredients to be assessed.

In the overall analysis, the G-BA establishes the continuation of the treatment with bevacizumab started with platinum-based first-line chemotherapy as the appropriate comparator therapy for olaparib in combination with bevacizumab.

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

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 olaparib in combination with bevacizumab is assessed as follows:

Hint for a considerable additional benefit.

Justification:

For the proof of additional benefit of olaparib in combination with bevacizumab, the pharmaceutical company presented the results of the PAOLA-1 study.

PAOLA-1 is a multicentre, double-blind, randomised controlled trial comparing olaparib in combination with bevacizumab to bevacizumab. The currently ongoing study, which started in July 2015, enrolled adult patients with advanced (FIGO stages III - IV) high-grade serous or endometrioid ovarian carcinoma, fallopian tube carcinoma and/or primary peritoneal carcinoma who showed a response (complete or partial) after platinum/taxane treatment as part of first-line chemotherapy regimen in combination with bevacizumab. The inclusion of the patients was independent of the status of the tumour with regard to homologous recombination deficiency (HRD status). Patients should have received at least 6 cycles of platinum/taxane treatment within a first-line chemotherapy regimen, of which at least the last 3 cycles were given in combination with bevacizumab. During first-line treatment and until randomisation, patients were not allowed to show any sign of progression of the underlying disease.

Furthermore, patients should have an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 or 1 for enrolment in the study. Side effects from previous chemotherapy had to have resolved to a Common Terminology Criteria for Adverse Event (CTCAE) grade ≤ 1.

The 806 patients enrolled were randomised 2:1 to the intervention arm (olaparib + bevacizumab) and to the comparator arm (bevacizumab), stratified by tumour BRCA gene (tBRCA) mutational status (mutated vs non-mutated) and first-line therapy outcome. The latter stratification characteristic was differentiated into 4 severities: Patients without detectable tumour after primary surgery (NED [PDS]), patients without detectable tumour/ with complete response after interval debulking surgery (NED/CR [IDS]), patients without detectable tumour/with complete response after chemotherapy (NED/CR [chemo]), and patients with partial response (PR).

According to the approved therapeutic indication of olaparib in combination with bevacizumab, those patients in a sub-population of the PAOLA-1 study whose tumour is associated with a positive HRD status are relevant for the present assessment. A positive HRD status is defined by a BRCA1/2-mutation and/or genomic instability. In the PAOLA-1 study, the Genomic Instability Score (GIS) was determined in tissue samples from all patients using the Myriad MyChoice HRD plus assay. Evaluations of a sub-population with a positive HRD status were submitted by the pharmaceutical company in the benefit assessment, whereby this was defined as a genomic instability with a GIS ≥ 42 and/or a pathogenic BRCA mutation in the tumour. This sub-population includes 387 patients (N = 255 in the intervention arm; N = 132 in the comparator arm) and is used for the present assessment.

Treatment with the study medication should be given for up to 2 years, until disease progression or discontinuation for other reasons, e.g. due to AE or patient choice. Treatment could also be continued beyond the intended 2 years, or in the case of disease progression, for as long as the patients had clinical benefit as judged by the principal investigator. According to the study protocol, there were no specifications regarding subsequent treatments after the end of the study medication.

With regard to prior surgical therapy, in the relevant sub-population of the PAOLA-1 study, the percentage of patients with primary surgery (PDS) is approximately 58%, while the

percentage of patients with interval debulking surgery (IDS) is approximately 37%. No previous surgery was performed in about 5% of the patients.

The PAOLA-1 study is being conducted in 137 study sites across Asia and Europe.

For the benefit assessment, the data cut-off of 22 March 2020, which corresponds to the a priori planned interim analysis for overall survival was submitted for the endpoint categories of morbidity, health-related quality of life and side effects (except for the specific AEs AML and MS).

For the endpoint of overall survival and the specific AEs AML and MS, the final data cut-off was submitted on 22 March 2022.

The results of the data cut-offs of 22 March 2020 and 22 March 2022 are used for the present benefit assessment.

Extent and probability of the additional benefit

Mortality

Overall survival is defined in the PAOLA-1 study as the time between randomisation and death, regardless of the underlying cause of death.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of olaparib in combination with bevacizumab in the assessment-relevant sub-population (with positive HRD status).

The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

There is an effect modification by the characteristic "outcome of first-line therapy" for overall survival. Since a homologous data basis exists for a combined consideration of the subgroups of patients without detectable tumour after primary surgery (NED [PDS]) and patients without detectable tumour/with complete response after chemotherapy (NED/CR [chemo]) on the one hand, and patients without detectable tumour/with complete response after interval debulking surgery (NED/CR [IDS]) and patients with partial response (PR) on the other hand, the respective results from a corresponding meta-analysis for these combined subgroups are considered. Accordingly, for the former patients (NED [PDS] and NED/CR [chemo]) there is a statistically significant effect to the advantage of olaparib in combination with bevacizumab. For the latter patients (NED/CR [IDS] and PR), however, there was no significant difference between the treatment groups.

When interpreting this result, significant uncertainties come into play.

The clinical relevance of the subgroups described appears uncertain, especially against the background of the assessments of clinical experts presented in the present written statement procedure. In this regard, the lack of clear data regarding the prognostic and predictive relevance of the outcome of interval debulking from German study sites also complicates a conclusive classification of the clinical relevance of the described subgroup feature. In addition, there are uncertainties regarding the methodological reliability of the delimitability of the respective patient groups. According to clinical experts, after debulking surgery has been performed, there is an inaccuracy in distinguishing between scar tissue and residual tumour based on imaging techniques. In this context, according to clinical experts, remission status is not currently used as a predictive factor.

Against the background of the uncertainties described above, the existing data basis on the observed effect modification by the characteristic "outcome of first-line therapy" in the present operationalisation are not considered sufficient to derive corresponding separate statements on the additional benefit in the overall assessment with the necessary certainty.

Morbidity

Progression-free survival 1 (PFS1)

PFS1 represents the primary endpoint of the PAOLA-1 study. It is operationalised as time from randomisation to objective disease progression according to modified RECIST criteria version 1.1 or death from any cause. Olaparib in combination with bevacizumab has a statistically significant prolonged PFS1 compared to bevacizumab.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The mortality endpoint component is already assessed via the overall survival endpoint as an independent endpoint. The morbidity component of disease progression is assessed according to RECIST criteria and thus not symptom-related, but by means of imaging procedures.

This procedure does not correspond to the recommendations in this therapeutic indication. Therefore, according to the German S3 guideline, no routine instrumental diagnostics or marker determination should be performed in symptom-free patients, since no prolongation of overall survival is expected with an earlier start of subsequent therapy. Only when symptoms are present should subsequent therapy be initiated.

Taking into account the aspects listed, the endpoint PFS1 is not used for the benefit assessment.

Progression-free survival 2 (PFS2)

PFS2 in the PAOLA-1 study is defined as the time from randomisation to the second disease progression (assessed by the respective routine method (including imaging), CA-125[2]measurement or progression based on symptoms) or death of any cause.

Olaparib in combination with bevacizumab has a statistically significant prolonged PFS2 compared to bevacizumab.

The PFS2 endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The mortality endpoint component is already assessed via the overall survival endpoint as an independent endpoint.

The morbidity component of disease progression of the endpoint PFS2 was assessed by imaging techniques, by laboratory parametric measurements (CA-125 measurement or by symptoms (symptomatic progression). No information is available on the percentage of patients in whom symptomatic progression was reported as the reason for diagnosis. In addition, as already discussed for the endpoint PFS1, no routine instrumental diagnostics as well as no marker determination, in particular no determination of the CA-125 level, should be performed in symptom-free patients in the present therapeutic indication. Taking into account the aspects listed, the endpoint PFS2 is not used for the benefit assessment.

[2] Cancer Antigen - 125

Recurrences

For the benefit assessment, the pharmaceutical company submitted results on recurrence rates and recurrence-free survival (RFS).

The assessments are based on surveys of a sub-population of those patients who showed a complete response at randomisation after primary therapy consisting of surgery and platinum-based chemotherapy in combination with bevacizumab. Complete response was defined as the absence of target or non-target lesions (as determined by radiological examination). Thus, this sub-population included the NED [PDS], NED/CR [IDS], and NED/CR [chemo]) subgroups, which accounted for approximately 81% of patients with positive HRD status.

Recurrences (RFS and recurrence rates) were operationalised as the time from randomisation to objectively detected recurrence (modified RECIST criteria version 1.1) or death from any cause, whichever occurred earlier. The pharmaceutical company assumes a curative therapeutic approach and interprets the occurrence of a relapse as a failure of a healing attempt.

According to the generally recognised state of medical knowledge, a relapse or progression event is to be assumed in the further course of the disease in the vast majority of patients in the present therapeutic indication. Several studies[3,4] show a high rate of relapse after platinum treatment as part of first-line chemotherapy regimen even after complete clinical or pathologic complete response.

The results of the PAOLA-1 study also show a high recurrence rate of approximately 76% after approximately 4.5 years or 79% after approximately 6.5 years of study duration in patients with a complete response at randomisation in the comparator arm.

It is also clear from the assessments presented by clinical experts in the present written statement procedure that it is currently not possible to conclusively assess the extent to which a curative situation could also arise in the present therapeutic indication area through the use of olaparib in combination with bevacizumab in maintenance treatment.

The results for the endpoints of recurrence rate and RFS are therefore not used in the present assessment.

Symptomatology

The symptomatology will be assessed in the PAOLA-1 study using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30 and the disease-specific additional module for ovarian carcinoma EORTC QLQ-OV28.

For the endpoints of EORTC QLQ-C30 and EORTC QLQ-OV28, the pharmaceutical company submits responder analyses with the operationalisations "time to first clinically relevant deterioration" and "time to permanent clinically relevant deterioration" without subsequent survey with a score below the respective response threshold compared to baseline.

[3] Chen H, Fang F, Liu GJ, Xie HY, Zou J, Feng D. Maintenance chemotherapy for ovarian cancer. Cochrane Database Syst Rev 2013; (6): CD007414

[4] Coleman RL, Monk BJ, Sood AK, Herzog TJ. Latest research and treatment of advanced-stage epithelial ovarian cancer. Nat Rev Clin Oncol 2013; 10(4): 211-224

Patient-reported endpoints were collected over 2 years after start of the study, regardless of disease progression. The median duration of observation in both treatment arms is 24 months, although it is unclear how this was calculated.

Both operationalisations submitted by the pharmaceutical company are patient-relevant. Equal median observation times were reported in the two treatment arms. In the course of the study, however, there is a continuous decline in the proportion of completed questionnaires. This decline cannot be explained solely by the patients deceased during the observation period. Already after 12 months, the percentage of completed questionnaires is approx. 67% in the intervention arm and 63% in the control arm. The decreasing percentage continues more strongly in the 2nd year, whereby high differential differences (≥ 10%) can be observed. Overall, it cannot be safely assumed that the observation periods are sufficiently equal over the course of the study. Against this background, the "time to first clinically relevant deterioration" is used in the present data basis.

For EORTC QLQ-C30 and -OV28, the pharmaceutical company submits both responder analyses for the time to deterioration by ≥ 10 points and those for the time to deterioration by ≥ 15 points in the dossier for the benefit assessment.

However, as for EORTC QLQ-C30 and EORTC QLQ-OV28 the evaluation with a response threshold of 10 points is a sufficient approximation to an evaluation with a response threshold of 15% (15 points), these are used for the present assessment.

Based on these evaluations, a statistically significant difference to the advantage of olaparib in combination with bevacizumab is shown for the endpoints "insomnia", "hormonal symptoms" as well as "side effects of chemotherapy". For the endpoints "nausea and vomiting" and "loss of appetite", there is a statistically significant difference to the disadvantage of olaparib in combination with bevacizumab.

In the overall analysis of the results, there is no predominant advantage or disadvantage with regard to the symptomatology.

Health status (EQ-5D, visual analogue scale)

The general health status is assessed by means of the EQ-5D visual analogue scale.

For the benefit assessment, the pharmaceutical company submits responder analyses with the operationalisations "time to first clinically relevant deterioration" and "time to permanent clinically relevant deterioration" without subsequent survey with a score below the respective response threshold compared to baseline.

Patient-reported endpoints were collected over 2 years after start of the study, regardless of disease progression.

For the present assessment, as already discussed, the analyses on the "time to first clinically relevant deterioration" are used.

In addition, the pharmaceutical company submits responder analyses for time to deterioration by ≥ 7, 10 and 15 points of VAS score from baseline. The evaluation for deterioration by ≥ 15 points is used for the assessment.

There are no statistically significant differences between the treatment arms in this case. There is therefore neither an advantage nor a disadvantage in terms of health status.

Quality of life

Health-related quality of life is assessed in the PAOLA-1 study using the functional scales of the disease-specific questionnaire EORTC QLQ-C30 as well as scales of the disease-specific additional module for ovarian carcinoma EORTC QLQ-OV28.

For the benefit assessment, the pharmaceutical company submits responder analyses with the operationalisations "time to first clinically relevant deterioration" and "time to permanent clinically relevant deterioration" without subsequent survey with a score below the respective response threshold compared to baseline.

Patient-reported endpoints were collected over 2 years after start of the study, regardless of disease progression.

For the present assessment, as already discussed, the analyses on the "time to first clinically relevant deterioration" by ≥ 10 points are used.

For all other endpoints no statistically significant difference was detected between the treatment groups.

In the overall analysis of the results, there are no relevant differences with regard to health-related quality of life in the sub-population relevant to the evaluation.

Side effects

Adverse events (AEs)

Almost all participants in the PAOLA-1 study experienced adverse events. The results for the endpoint "total adverse events" are only presented additionally.

Serious adverse events (SAEs)

For the serious adverse events, there was no statistically significant difference between the treatment arms.

Severe AEs (CTCAE grade ≥ 3)

For serious adverse events with CTCAE grade ≥ 3, there is no statistically significant difference between the treatment groups.

Discontinuation due to AEs

For the endpoint therapy discontinuation due to an AE, there is a statistically significant difference to the disadvantage of olaparib in combination with bevacizumab compared to bevacizumab.

Specific AEs

There is a statistically significant disadvantage for olaparib in combination with bevacizumab compared to bevacizumab with regard to the specific AE nausea (PT) as well as the specific severe AE (CTCAE grade ≥ 3) anaemia (PT) and fatigue (PT). For the specific severe AE (CTCAE grade ≥ 3) hypertonia (PT), there is a statistically significant advantage for olaparib in combination with bevacizumab.

For the endpoints of myelodysplastic syndrome and acute myeloid leukaemia, there is no statistically significant difference between the treatment groups in each case.

The overall assessment of the results on side effects shows a disadvantage for olaparib in combination with bevacizumab in the endpoint of discontinuation due to AEs. In detail, there are predominantly negative effects of olaparib in combination with bevacizumab compared to bevacizumab for the specific AEs.

Overall assessment

For the assessment of the additional benefit of olaparib in combination with bevacizumab, results are available from the double-blind, randomised controlled trial PAOLA-1 in comparison to bevacizumab for mortality (overall survival), morbidity (symptomatology and health status), quality of life and side effects.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of olaparib in combination with bevacizumab in the assessment-relevant sub-population (with positive HRD status).

The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

For the endpoints of the morbidity category, treatment with olaparib in combination with bevacizumab resulted in both positive effects regarding the endpoints of insomnia, hormonal symptomatology and side effects of chemotherapy (assessed by EORTC QLQ-C30 and EORTC QLQ-OV28) and negative effects regarding the endpoints of nausea and vomiting as well as loss of appetite. With regard to the symptomatology, there is therefore no predominant advantage or disadvantage in the overall analysis.

For the endpoint of general health status (assessed by EQ-5D VAS), there is no statistically significant difference between the treatment groups.

For health-related quality of life (assessed by EORTC QLQ-C30 and EORTC QLQ-OV28), there are no relevant differences between treatment with olaparib in combination with bevacizumab compared to bevacizumab.

With regard to the endpoint category of side effects, there is a disadvantage for olaparib in combination with bevacizumab in the endpoint of discontinuation due to AEs. In detail, there are predominantly negative effects of olaparib in combination with bevacizumab compared to bevacizumab for the specific AEs.

In the overall assessment, the G-BA identified a considerable additional benefit of olaparib in combination with bevacizumab.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of a double-blind, randomised, multicentre study.

The risk of bias across all endpoints is rated as low.

The risk of bias of the results on overall survival, symptomatology, health status, health-related quality of life is rated as low.

For the endpoint of overall survival, however, there are significant uncertainties regarding the clinical relevance of the present effect modification by the characteristic "outcome of first-line therapy".

Therefore, in the overall assessment, the reliability of data for the additional benefit determined is classified in the category "hint".

2.1.4 Summary of the assessment

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

"Lynparza in combination with bevacizumab is indicated for the:

maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status is defined by either a BRCA1/2-mutation and/or genomic instability."

Continuation of treatment with bevacizumab initiated with platinum treatment as part of first-line chemotherapy regimen was determined to be the appropriate comparator therapy.

The pharmaceutical company presents results from the double-blind, randomised controlled PAOLA-1 trial comparing olaparib in combination with bevacizumab to bevacizumab. For the present benefit assessment, the relevant sub-population is the one whose tumour is associated with a positive HRD status.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of olaparib in combination with bevacizumab over bevacizumab. The magnitude of the effect is assessed as a significant improvement. For the endpoint of overall survival, however, there are significant uncertainties regarding the clinical relevance of the present effect modification by the characteristic "outcome of first-line therapy".

In the morbidity (symptomatology) category, there is no predominant advantage or disadvantage. There is no statistically significant difference between the treatment arms regarding general health status.

For health-related quality of life, there are no relevant differences between the treatment groups.

With regard to the endpoint category of side effects, there is a disadvantage for olaparib in combination with bevacizumab in the endpoint of discontinuation due to AEs. In detail, there are predominantly negative effects of olaparib in combination with bevacizumab compared to bevacizumab for the specific AEs.

In the overall assessment, the G-BA identified a hint for a considerable additional benefit of olaparib in combination with bevacizumab.

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

Adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status (defined by either a BRCA1/2-mutation and/or genomic instability); maintenance therapy

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 current information from the dossier of the pharmaceutical company. It must be taken into account that uncertainties exist with regard to the percentage value of the patients with positive HRD status. In addition, the number of patients could increase if all patients eligible for platinum-based treatment as part of first-line chemotherapy regimen in combination with bevacizumab are included.

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 Lynparza (active ingredient: olaparib) at the following publicly accessible link (last access: 13 April 2023):

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

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

Prior to initiating treatment with Lynparza and bevacizumab for first-line maintenance treatment of epithelial ovarian carcinoma (EOC), fallopian tube carcinoma (FTC), or primary peritoneal carcinoma (PPC), patients must have a confirmed or suspected harmful BRCA1/2-mutation and/or genomic instability as determined by a validated testing 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 April 2023).

Treatment period:

The costs for the first year are presented.

Administration of bevacizumab is limited to a maximum period of 15 months (including administration in combination with platinum treatment as part of first-line chemotherapy regimen). In 15 months, a total of 21.7 cycles every three weeks is possible. After deduction of the 6 cycles of bevacizumab in combination with the platinum treatment as part of first-line chemotherapy regimen, as mentioned in the product information, 15.7 cycles of bevacizumab in combination with olaparib remain in the present treatment setting. Only these are used for the calculation of the annual treatment costs.

Since the administration of olaparib is limited to a maximum of 2 years, a 365-day intake is used as a basis for this active ingredient.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Olaparib	Continuously, 2 x daily	365	1	365
Bevacizumab	1 x every 21 days	15.7	1	15.7
Appropriate comparator therapy				
Bevacizumab	1 x every 21 days	15.7	1	15.7

Consumption:

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

The active ingredient bevacizumab is administered according to body weight. For doses according to body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied. Taking into account the therapeutic indication, an average body weight of adult women is used for the calculation of consumption (68.7 kg).[5]

As it is not possible to achieve the exact calculated dose per cycle with the commercially available dose strengths, in these cases the dose is rounded up to the next higher available dose.

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Olaparib	300 mg	600 mg	4 x 150 mg	365	1,460 x 150 mg

[5] Microcensus (2017): questions on health - body measurements of the population: https://www.gbe-bund.de/gbe10/pkg_isgbe5.prc_isgbe?p_uid=gast&p_aid=0&p_sprache=D (accessed 16.04.2021).

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Bevacizumab	15 mg/kg = 1,030.50 mg	1030.50 mg	2 x 400 mg + 3 x 100 mg	15.7	31.4 x 400 mg + 47.1 x 100 mg
Appropriate comparator therapy					
Bevacizumab	15 mg/kg BW = 1,030.50 mg	1030.50 mg	2 x 400 mg + 3 x 100 mg	15.7	31.4 x 400 mg + 47.1 x 100 mg

Costs:

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

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Olaparib 150 mg	112 FCT	€ 4,945.66	€ 2.00	€ 478.56	€ 4,465.10
Bevacizumab 400 mg	1 CIS	€ 1,553.30	€ 2.00	€ 146.43	€ 1,404.87
Bevacizumab 100 mg	1 CIS	€ 396.98	€ 2.00	€ 36.61	€ 358.37
Appropriate comparator therapy					
Bevacizumab 400 mg	1 CIS	€ 1,553.30	€ 2.00	€ 146.43	€ 1,404.87
Bevacizumab 100 mg	1 CIS	€ 396.98	€ 2.00	€ 36.61	€ 358.37
Abbreviations: CIS = concentrate for the preparation of an infusion solution, FCT = film-coated tablets					

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Costs for additionally required SHI services:

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

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

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

Other SHI services:

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

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

2.5 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 Olaparib

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.

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

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

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 10 December 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 28 October 2022, the pharmaceutical company submitted a dossier for the benefit assessment of olaparib to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 5 VerfO.

By letter dated 31 October 2022 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 olaparib.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 January 2023, and the written statement procedure was initiated with publication on the G-BA website on 1 February 2023. The deadline for submitting written statements was 22 February 2023.

The oral hearing was held on 6 March 2023.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 13 April 2023, and the proposed resolution was approved.

At its session on 20 April 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 December 2019	Determination of the appropriate comparator therapy
Working group Section 35a	28 February 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	6 March 2023	Conduct of the oral hearing
Working group Section 35a	14 March 2023 4 April 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	13 April 2023	Concluding discussion of the draft resolution
Plenum	20 April 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 April 2023

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

Prof. Hecken