Justification

Gemeinsamer Bundesausschuss

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Olaparib (New Therapeutic Indication: Ovarian carcinoma, fallopian tube carcinoma or primary peritoneal carcinoma; maintenance treatment after first-line therapy; HRD-positive; combination with bevacizumab)

of 3 June 2021

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 submission 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:

1st approved therapeutic indication,

2nd medical benefits,

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

4th Number of patients and patient groups for whom there is a therapeutically significant additional benefit,

5th Costs of therapy for the statutory health insurance,

6th 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 olaparib (Lynparza) was listed for the first time in the Great German Specialties Tax (Lauer Tax) on 1 June 2015.

On 3 November 2020, olaparib received marketing authorisation for a new therapeutic indication to be classified as a major type 2 amendment 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 amendments to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 30 November 2020, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient Olaparib with the new therapeutic indication “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 chemotherapyin 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." submitted.

The G-BA commissioned IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 March 2021 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. An oral hearing was also 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, as well of the addendum drawn up by the G-BA on the benefit assessment. In order to determine the extent of the additional benefit, the G-BA has assesses 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 chemotherapyin 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 3/6/2021):

see 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 carcinoma, fallopian tube carcinoma, or primary peritoneal carcinoma who have a response (complete or partial) after completion of a platinum treatment as part of first-line chemotherapy regimen in combination with bevacizumab; disease associated with homologous recombination deficiency (defined by either a BRCA1/2-mutation and/or genomic instability); maintenance treatment:

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.

[1] General Methods, version 6.0 of 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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 Federal Joint Committee shall be preferred.
4. The comparator therapy should be part of the appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge.

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

on 1. Medicinal products with the following active ingredients are approved for the present therapeutic indication:

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 are available for medicinal product treatment in the present therapeutic indication:

Resolution 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. 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 health care provision.

The generally accepted state of medical knowledge for the indication was established by means of a systematic search for guidelines and reviews of clinical studies.

Therefore, overall, there is limited evidence for maintenance treatment of advanced high-grade epithelial ovarian carcinoma, fallopian tube carcinoma, or primary peritoneal carcinoma with tumours with a positive status of homologous recombination deficiency (BRCA1/2-mutation and/or genomic instability) after prior platinum treatment as part of first-line chemotherapy regimen.
Specifically, the national S3 guideline[2] for the primary treatment of patients in the present therapeutic indication strongly recommends first-line chemotherapy. With

[2] Guideline program in oncology (German Cancer Society, German Cancer Aid, Association of the Scientific Medical Societies). S3 guideline Diagnostics, therapy and aftercare of malignant ovarian tumours; long version 4.0 [online]. AWMF Register Number: 032/035OL.

regard to possible chemotherapeutic maintenance treatments, the guidelines further state that these should not be carried out after completion of the primary treatment. The additional administration of bevacizumab in combination with primary chemotherapy and henceforth as maintenance treatment can be considered according to the S3 guideline. According to the authorisation status, maintenance treatment with bevacizumab can be considered if the primary treatment 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, the PARP inhibitor olaparib is available as monotherapy, approved for the maintenance treatment of advanced BRCA1/2-mutated high-grade epithelial ovarian carcinoma (with response after completed platinum treatment as part of first-line chemotherapy regimen). In its resolution of 16 January 2020, the G-BA did not determine any additional benefit in the benefit assessment of olaparib in this indication compared to monitoring wait-and-see approach. The resolution is valid until 1 April 2024. The therapeutic value of olaparib cannot be conclusively assessed at present.

In addition, on 27 October 2020, the PARP inhibitor niraparib was approved for the maintenance treatment of advanced high-grade epithelial ovarian cancer, fallopian tube carcinoma or primary peritoneal carcinoma (with response after platinum treatment as part of first-line chemotherapy regimen). In its resolution of 20 May 2021, the G-BA, against the background that no complete study data were available for the benefit assessment, did not determine an additional benefit of niraparib in this therapeutic indication compared with the appropriate comparator therapy. Niraparib is currently not eligible as an appropriate comparator therapy.

According to the present therapeutic indication, olaparib in combination with bevacizumab is used in patients with a response (complete or partial) after platinum treatment as part of first-line chemotherapy regimen in combination with bevacizumab. For this specific situation, the G-BA specifies the continuation of treatment with bevacizumab started with platinum treatment as part of first-line chemotherapy regimen as an appropriate comparator therapy.

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

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:

An additional benefit of olaparib in combination with bevacizumab compared to bevacizumab has not been proven.

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 multi-centre, double-blind, randomised controlled trial comparing olaparib in combination with bevacizumab to bevacizumab. The currently ongoing study, which started in July 2015, included 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 inclusion. Side effects from previous chemotherapy had to have resolved to a Common Terminology Criteria for Adverse Event (CTCAE) grade ≤ 1.

The 806 patients included were randomised 2:1 to the intervention arm (olaparib + bevacizumab) and to the comparator arm (bevacizumab), stratified by tumour BRCA gene (tBRCA) mutation status (mutated vs. non-mutated) and first-line therapy outcome. The latter stratification characteristic was differentiated into 4 expressions: Patients without detectable tumour after primary surgery (NED [PDS]), patients without detectable tumour/with complete response after interval 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 benefit assessment. A positive HRD status is defined by a BRCA1/2-mutation and/or genomic instability. In PAOLA-1, 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 study physician. According to the study protocol, there were no specifications regarding subsequent treatments after the end of the study medication.

With regard to surgical pre-treatment, in the relevant sub-population of the PAOLA-1 study, the proportion of patients with primary surgery (PDS) is approximately 58%, while the proportion of patients with interval surgery (IDS) is approximately 37%. No previous surgery was performed in about 5% of the patients. In the German health care context primary surgery with the aim of an early maximum reduction of tumour tissue (debulking) is clearly preferred to interval surgery, as can also be seen from the benefit assessment presented in the written statement procedure, therefore, compared to the described sub-population of PAOLA-1 in Germany, a relevantly higher proportion of patients with primary surgery can be assumed.

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

The data cut-off of 22 March 2020 was submitted for the benefit assessment, which corresponds to the a previous planned interim analysis for overall survival. This analysis was planned to coincide with the final PFS2 analysis, which was scheduled after 411 events for the PFS or no later than 1 year after the final PFS analysis (dated 22 March 2019). The results of this data cut-off on 22 March 2020 are used for this benefit assessment.
The final analysis of overall survival is planned from a data maturity of approximately 60% or at the latest 3 years after the final analysis of PFS.

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 Overall survival, there was no statistically significant difference between the treatment groups in the sub-population relevant to the evaluation (with positive HRD status).

There is an effect modification by the "outcome of first-line therapy" feature for overall survival. Since a homologous data situation 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 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 in favour 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, the following relevant uncertainties come into play.
On the one hand, there is only a small number of events in the sub-population relevant to the evaluation and in the subgroups considered. The median survival has not yet been reached, final analysis on the endpoint overall survival are pending.
On the other hand, 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 centres also complicates a conclusive classification of the clinical relevance of the described subgroup feature. Furthermore, 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.

No additional benefit is identified for the Overall survival endpoint. Against the background of the uncertainties described above, the existing data basis on the observed effect modification by the feature "outcome of first-line therapy" 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[3]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 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 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 proportion 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.

Relapse

In the dossier, the pharmaceutical company describes endpoints on the complex "relapses" and presents results on relapse rates and relapse-free survival (RFS) based on a sub-population.

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 treatment platinum treatment as part of chemotherapy regimen. 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.

Regarding the operationalisation, the pharmaceutical company submits the information that the operationalisation of the RFS corresponded to that of the PFS. Accordingly, modified RECIST criteria version 1.1 were used, which allowed the assessment of progression due to new lesions in patients without tumour evidence at baseline. The relapse rate was defined as the proportion of patients with relapse or death. The pharmaceutical company assumes a curative therapy 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[4,5] show a high rate of relapse after platinum

[3] Cancer Antigen - 125

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

[5] 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

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 relapse rate of approximately 76% after approximately 4.5 years of study 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 on the complex “relapses” are therefore not used in the present assessment.

Symptomatology

Symptoms 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. The assessment will be conducted regularly (every 12 weeks) in the study for 2 years until the data cut-off of the primary analysis and at the end of the study medication. After the progression of the disease assessment is carried out every 12 weeks.

For EORTC QLQ-C30 and -OV28, the pharmaceutical company submitted responder analysis for time to worsening (defined as an increase in score of at least 10 points from baseline) in the dossier for the benefit assessment.

Within the framework of the written statement procedure on the present benefit assessment, the pharmaceutical company submitted additional responder analysis on EORTC QLQ-C30 and EORTC QLQ-OV28 using a response threshold of 15% of the scale range.

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), the analysis presented in the dossier for the benefit assessment 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 consideration of the results, there is no predominant advantage or disadvantage with regard to the symptomatology.

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

The general state of health is assessed by means of the EQ-5D visual analogue scale. The assessment will be conducted regularly (every 12 weeks) in the study for 2 years until the data cut-off of the primary analysis and at the end of the study medication. After the progression of the disease assessment is carried out every 12 weeks.

For the benefit assessment, the pharmaceutical company submitted responder analysis for the time to worsening by ≥ 7 or 10 points of the VAS score compared to baseline and continuous evaluations (analysis of mean differences).

IQWIG’s dossier assessment uses analysis of mean differences. In addition, the responder analysis were presented in the addendum of the dossier assessment. The mean difference between the treatment groups was not statistically significant.

Within the framework of the written statement procedure on the present benefit assessment, additional responder analysis were submitted by the pharmaceutical company using a response threshold of ≥ 15 points.

The study on which the derivation of the minimal important difference (MID) for the responder analysis is based (Pickard et al., 2007) is not considered by IQWiG to be appropriate for demonstrating the validity of the MID. This is justified on the one hand by the fact that the aforementioned work does not contain a longitudinal study to determine the MID, which is assumed in the current scientific discussion to derive a valid MID. Furthermore, the anchors ECOG-PS and FACT-G sum score used in the study are also not considered by IQWiG to be appropriate for deriving an MID.
In view of the fact that responder analysis based on a MID for a clinical assessment of effects generally have advantages over an analysis of standardised mean differences, and taking into account that the validation study in question has already been used in previous evaluations, the G-BA uses the responder analysis for the evaluation of the effects on symptomatology in the present evaluation.

Here, for the three response criteria (≥ 7, ≥ 10 and ≥ 15 points), there are no statistically significant differences between the treatment groups. 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. The assessment will be conducted regularly (every 12 weeks) in the study for 2 years until the data cut-off of the primary analysis and at the end of the study medication. After the progression of the disease assessment is carried out every 12 weeks.

For EORTC QLQ-C30 and -OV28, the pharmaceutical company submitted responder analysis for time to worsening (defined as a decrease (for EORTC QLQ-C30) or increase (for EORTC QLQ-OV28) in score by at least 10 points from baseline) in the dossier for the benefit assessment.

Within the framework of the written statement procedure on the present benefit assessment, the pharmaceutical company submitted additional responder analysis on EORTC QLQ-C30 and EORTC QLQ-OV28 using a response threshold of 15% of the scale range.

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), the analysis presented in the dossier for the benefit assessment are used for the present assessment.

For the endpoint “Permanent ventilation” no statistically significant difference was detected between the treatment groups. However, for this endpoint there is an effect modification by the “age” feature, according to which there is a statistically significant effect in favour of olaparib in combination with bevacizumab for patients ≥ 65 years, whereas there is no difference between the treatment groups for patients < 65 years.

For the endpoint “Attitude towards disease/treatment” there is also no statistically significant difference between the treatment groups. For this endpoint, however, an effect modification is shown by the feature “outcome of first-line therapy”. Accordingly, for patients in the subgroup NED/CR [IDS], there is a statistically significant effect to the disadvantage of olaparib in combination with bevacizumab. For patients in the subgroups NED [PDS], NED/CR [chemo] and PR there is no difference between the treatment groups.

For the endpoint “Hospitalisation” 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 (AE)

The AE is assessed up to 30 days after the end of treatment.

Serious adverse events (SAE)

SAEs are assessed up to 30 days after the end of treatment.

For the endpoint Serious respiratory adverse events no statistically significant difference was detected between the treatment arms.

Severe AE (CTCAE grade ≥ 3)

The assessment of severe AEs *(*CTCAE grade ≥ 3) is performed up to 30 days after the end of treatment.

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

Discontinuation due to AE

For the endpoint Infections and infestations, there is a statistically significant difference to the disadvantage of olaparib + bevacizumab compared to bevacizumab.

Specific AE

For selected specific AE, an assessment will be conducted in the PAOLA-1 study until death or final analysis. This extended survey period applies to all specific AEs considered in this assessment.

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 and asthenia (PT). For the specific severe AE (CTCAE grade ≥ 3) hypertonia (PT), there is a statistically significant advantage for olaparib in combination with bevacizumab.

In view of the reference in IQWiG's dossier assessment to the summarised evaluation of the specific AE myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) in the dossier, additional separate evaluations of the specific AE MDS and AML were submitted by the pharmaceutical company during the comments procedure on the present benefit assessment.

Neither the pooled analysis of the endpoint MDS and AML (PT) nor the separate analysis of the two endpoints MDS and AML show a statistically significant difference between the treatment groups.

Overall, there was no statistically significant difference in side effects between the treatment groups with respect to the endpoints Serious AEs and Severe adverse events (CTCAE grade ≥ 3). For the endpoint Discontinuation due to AE, there is a disadvantage of olaparib in combination with bevacizumab. In detail, the specific AEs show predominantly negative effects of olaparib in combination with bevacizumab compared to bevacizumab.

Overall assessment

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

In the endpoint category mortality, the available results for the endpoint overall survival related to the sub-population relevant for the assessment (with positive HRD status) show no statistically significant difference. Final analyses from the PAOLA-1 study on the endpoint of overall survival are pending. No additional benefit is identified for the Overall survival endpoint.

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

There is no statistically significant difference in side effects between the treatment groups with respect to the endpoints serious AEs and severe adverse events (CTCAE grade ≥ 3). For the endpoint discontinuation due to AE, there is a disadvantage of olaparib in combination with bevacizumab. In detail, the specific AEs show predominantly negative effects of olaparib in combination with bevacizumab compared to bevacizumab.

Taking into account the clinical relevance, the disadvantage in terms of side effects in view of the fact that moderate disadvantages were only shown for the endpoint discontinuation due to AEs as well as in detail for the specific AEs, however, does not reach a magnitude that would justify a lower benefit in the overall assessment.

Overall, the G-BA came to the conclusion that an additional benefit of olaparib in combination with bevacizumab compared to bevacizumab is not proven.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of olaparib finds its legal basis in Section 35a paragraph 3 sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment pursuant to Section 35a paragraph 1 SGB V.

The overall survival data available for this assessment from the PAOLA-1 study are preliminary with a small number of events at the time of this data cut-off. The final results from the study, which is still ongoing, are still pending.

Since clinical data concerning the overall survival are expected to be relevant for the assessment of the medicinal product, it is justified to limit the validity of the resolution until further scientific knowledge is available for the assessment of the additional benefit of olaparib. The limitation enables the expected interim results from the PAOLA-1 study to be included in the benefit assessment of the medicinal product in accordance with Section 35a SGB V in a timely manner.

For this purpose, the G-BA considers a limitation for the resolution until 1 October 2022 to be appropriate.

Conditions for the limitation:

For the new benefit assessment after expiry of the deadline, the results from the final analysis of overall survival and all other patient-relevant endpoints from the PAOLA-1 study that are expected for March 2022 are to be presented in the dossier.

A change in the time limit can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3 paragraph 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment of the medicinal product olaparib recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of olaparib in comparison with the appropriate comparator therapy (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). If the assessment is not submitted or is incomplete, the G-BA may determine that an additional benefit has not been proven.

The possibility that a benefit assessment for the medicinal product olaparib can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, nos. 2 – 4 VerfO) remains unaffected hereof.

2.1.5 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 chemotherapyin 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.”

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.

In the category mortality, there is no statistically significant difference between the two treatment groups. Final analysis for the endpoint overall survival are pending.

In the morbidity (symptomatology) category, there is no predominant advantage or disadvantage. There is no statistically significant difference for the general state of health.

No relevant differences are found for health-related quality of life.

In terms of side effects, the endpoint discontinuation due to AEs shows a disadvantage of olaparib in combination with bevacizumab. In detail, the specific AE show predominantly negative effects. However, taking into account the clinical relevance, the disadvantage in terms of side effects does not reach a level that would justify a lower benefit in the overall assessment.

In conclusion, the G-BA states that an additional benefit of olaparib in combination with bevacizumab compared to bevacizumab is not proven.

The validity of the resolution is limited to 1 October 2022.

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 based its resolution on the data from the dossier of the pharmaceutical company, whereby the consideration of a test rate with regard to the HRD status was waived, as the number of patients who are eligible for treatment with olaparib according to the marketing authorisation is relevant, irrespective of the proportion of tested patients. Furthermore, it must be taken into account that uncertainties exist with regard to the proportion value of a positive HRD status. In addition, the number of patients could increase if all patients eligible for platinum 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: 2 March 2021):

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

Treatment with olaparib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in gynaecology and obstetrics, and specialists participating in the Oncology Agreement who 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 information of the product information as well as the information in the Lauer-Taxe (status: 15 May 2021).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual treatment duration is patient-individual and/or is shorter on average.

Treatment duration:

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 is patient-individual 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.

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 therapy situation. 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.

Name of therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/ treatment (days)	Days of treatment/ patient/ Year
Medicinal product to be assessed				
Olaparib	continuously, twice a day	365	1	365
Bevacizumab	once every 21 days	15,7	1	15,7
Appropriate comparator therapy				
Bevacizumab	once every 21 days	15,7	1	15,7

Consumption:

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 application, an average body weight of adult women is used for the calculation of consumption (68.7 kg).[6]

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.

[6]Microcensus 2017: Microcensus 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 16/4/2021).

Name of therapy	Dosage/ Application	Dosage/patient/days of treatment	Usage by strength/day of treatment	Days of treatment/ 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
Bevacizumab	15 mg/kg bw = 1030.50 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 = 1030,50 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 Sections 130 and 130 a SGB V. For the calculation of the annual treatment costs, the required number of packs by strength was first determined on the basis of consumption. Having determined the number of packs of a particular strength, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Cost of medicinal product:

Name of therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Cost after deduction of statutory rebates
Medicinal product to be assessed					
Olaparib 150 mg	112 FCT	€ 5,616,98	€ 1,77	€ 317,51	€ 5,297,70
Bevacizumab 400 mg	1 IFK	€ 1,553,06	€ 1,77	€ 85,42	€ 1,465,87
Bevacizumab 100 mg	1 IFK	€ 396,75	€ 1,77	€ 21,35	€ 373,63
Appropriate comparator therapy					
Bevacizumab 400 mg	1 IFK	€ 1,553,06	€ 1,77	€ 85,42	€ 1,465,87
Bevacizumab 100 mg	1 IFK	€ 396,75	€ 1,77	€ 21,35	€ 373,63
Abbreviations: IFC = concentrate for the preparation of an infusion solution; FCT = film-coated tablets					

Stand Lauer-Taxe: 15 May 2021

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 when using the drug to be evaluated and the appropriate comparator therapy according to the product information, the costs incurred for this are to be taken into account as costs for additionally required SHI services.

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

As there are no regular differences in the necessary use of medical treatment or in the prescription of other services when using the medicinal product to be evaluated and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be considered.

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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), all surcharges for the production of parenteral preparations containing cytostatic drugs a maximum of €81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies a maximum of €71 per ready-to-use unit are to be payable. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating 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 sales 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 retail pharmacist services (Hilfstaxe).

3. Bureaucratic costs

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 30 November 2020, 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 2 VerfO.

By letter dated 30 November 2020 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 10 March 2021, and the written statement procedure was initiated with publication on the G-BA website on 15 March 2021. The deadline for submitting written statements was 6 April 2021.

The oral hearing was held on 27 April 2021.

By letter dated 28 April 2021, 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 12 May 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (WG 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 were discussed at the session of the subcommittee on 26 May 2021, and the draft resolution was approved.

At its session on 3 June 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	10 December 2019	Implementation of the appropriate comparator therapy
Working group Section 35a	20 April 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal product	27 April 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	4 May 2021 18 May 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal product	26 May 2021	Final discussion of the draft resolution
Plenum	3 June 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 3 June 2021

Federal Joint Committee
in accordance with Section 91 SGB V
The chairman

Prof. Hecken