Justification

Gemeinsamer Bundesausschuss

to 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: High-Grade Epithelial Ovarian Cancer, Fallopian Tube Cancer or Primary Peritoneal Cancer, BRCA Mutation, Maintenance Treatment)

of 16 January 2020

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 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 shall pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

On 12 June 2019, olaparib received marketing authorisation for a new therapeutic indication:

“Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) 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”.

On 10 July 2019, the pharmaceutical company 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 in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 October 2019, 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 arrived at 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 is indicated as monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) 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.

2.1.2 Appropriate comparator therapy

Adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) 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

- Monitoring wait-and-see approach

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 according to 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. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

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, paclitaxel, treosulfan, and melphalan.

On 2. No non-medicinal treatments are considered.

On 3. There are no resolutions on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V.

On 4. The generally state of medical knowledge for the indication was established by means of a systematic search for guidelines and reviews of clinical studies.

Accordingly, there is only limited evidence for maintenance treatment following previous platinum-based first-line chemotherapy of advanced BRCA-mutated high-grade epithelial ovarian cancer, tubal cancer, or primary peritoneal cancer. From the present guidelines, it cannot be deduced that maintenance treatment is regularly recommended in the present therapeutic indication. Specifically, the S3-guideline[2] for the primary treatment of patients in this therapeutic indication strongly recommends first-line chemotherapy. Regarding possible chemotherapeutic maintenance treatments, the guideline states that these should not be carried out after completion of the primary therapy. In accordance with the S3 guideline, the additional administration of bevacizumab in combination with primary chemotherapy and henceforth as maintenance treatment can be considered. According to the authorisation status, maintenance treatment with bevacizumab is considered if the primary therapy also included the use of bevacizumab. In the overall view, the G-BA therefore defines the monitoring wait-and-see approach as an appropriate comparator therapy in this therapeutic indication.

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of olaparib is assessed as follows:

For olaparib as monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) 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, an additional benefit is not proven.

Justification:

The pharmaceutical company submitted data on the benefit assessment of olaparib from the ongoing randomised, double-blind, placebo-controlled SOLO1 Phase III study.

At the start of the SOLO1 study, 391 adult patients with advanced (FIGO (Fédération-Internationale-de-Gynécologie-et-d'Obstétrique) Stage III or IV) high-grade serous or high-grade endometrioid ovarian cancer and an ECOG-PS ≤ 1 who had responded (completely or

[2] Guidelines Programme for Oncology (German Cancer Society, German Cancer Aid, Association of the Scientific Medical Societies). S3 guideline diagnosis, therapy and after-care of malignant ovarian tumours; long version 2.1 [on-line]. AWMF register number: 032/035OL.

partially) to previous platinum-containing first-line chemotherapy were included in the main cohort. 375 (approx. 96%) of the patients had tumours of serous histology, and 16 (approx. 4%) had tumours of non-serous histology. All patients had a mutation in the genes BRCA (Breast Cancer Susceptibility Gene) 1 or BRCA2. The patients were randomised at a ratio of 2:1 (olaparib N = 260; placebo N = 131) and stratified according to the response to platinum-based first-line chemotherapy (complete/partial).

The primary endpoint of the study is progression-free survival (PFS). Patient-relevant secondary endpoints are overall survival, health status, health-related quality of life, and adverse events.

Patients are treated until disease progression, unacceptable toxicity, or withdrawal of consent but no longer than up to two years. At the investigator's discretion, patients may continue to be treated with the study medication under these conditions (even after disease progression) as long as, in the investigator's view, they continue to benefit from the treatment and no other termination criteria are present.

The decision on the type of follow-up therapy after therapy discontinuation is at the investigator's discretion. However, according to the study design, a change from the placebo arm to treatment with olaparib is not permitted. Furthermore, although the unblinding of patients and investigators is not explicitly planned in connection with the initiation of follow-up therapy, 90 patients (23%) had already been unblinded at the time of this data cut-off.

The results presented by the pharmaceutical company in the dossier are based on the first, pre-planned data cut-off after about 196 progression events on 17 May 2018. The benefit assessment is based on this data cut-off. The final analysis of the overall survival endpoint is planned after 60% of events have occurred.

On the implementation of the appropriate comparator therapy

The guidelines recommend a symptom-oriented approach with physical and gynaecological examinations for the after-care of patients in this therapeutic indication. However, routine instrumental diagnostics or marker determination should not be performed in symptom-free patients. However, if a suspected relapse is due to an elevated cancer antigen 125 (CA-125) level, the further diagnostic procedure should be discussed individually with the patients. Also with regard to the initiation of follow-up therapies, the guidelines attach great importance to individual consultation and decision making with patients.

In the SOLO1 study, on the other hand, regular examinations using imaging techniques to diagnose a progression are planned; these will allow deviations in the implementation of the monitoring wait-and-see approach to be identified. However, in the SOLO1 study, it is at the discretion of the investigator whether to discontinue or continue treatment after progress in accordance with RECIST – and thus when to initiate follow-up therapy. As mentioned, 90 patients have been unblinded during the course of the study (olaparib: 38 [14.6%] patients; placebo: 52 [39.7%] patients) of which almost all after disease progression (34 [13.1%] in the olaparib arm and 51 [39.0%] in the control arm). This indicates that unblinding was also carried out with a view to initiating follow-up therapy and that the patients decided on follow-up therapies together with the investigator.

Despite remaining uncertainties, the monitoring wait-and-see approach of the SOLO1 study is considered to be adequate implementation of the appropriate comparator therapy.

<u>Extent and probability of the additional benefit</u>

<u>Mortality</u>

In the SOLO1 study, overall survival is defined as the time from randomisation to death of any cause.

As of 17 May 2018, a total of 82 patients had died: 55 in the intervention arm (21.2%) and 27 in the comparator arm (20.6%). The median survival time was not yet achieved in either study arm. The event time analysis shows no statistically significant difference between the treatment groups (hazard ratio (HR) = 0.95 [0.60, 1.53]; p value = 0.890). An additional benefit of olaparib is therefore not proven in the mortality category.

In this context, it should be noted that the results on the overall survival endpoint are still not very meaningful, especially because of the low event rates in the study arms and the relatively short observation period. The data basis therefore does not yet allow a final assessment of overall survival. The final analysis from the current study are still pending.

Morbidity

Progression-free survival 1 (PFS1)

PFS1 is the primary endpoint of the SOLO1 study. It is operationalised as the time from randomisation to objective disease progression according to RECIST or death of any cause. The median time to the event is 13.8 months in the comparator arm; in the intervention arm, the event has not yet been reached. Event time analysis shows a statistically significant effect in favour of olaparib (HR = 0.30 [0.23; 0.41]; p value < 0.0001).

The PFS1 is a combined endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component mortality is already surveyed via the endpoint overall survival as an independent endpoint. The morbidity component disease progression is assessed according to RECIST criteria and thus not in a symptom-related manner but rather by means imaging procedures.

This procedure does not correspond to the recommendations in this indication. According to the German S3 guideline[2], routine apparative diagnostics or marker determination should not be performed in symptom-free patients because no prolongation of overall survival is expected if follow-up therapy is initiated earlier. Only when the symptomatology is present should follow-up therapy be initiated.

In consideration of the aspects listed, the endpoint PFS1 is not used for the benefit assessment.

Progression-free survival 2 (PFS2)

In the SOLO1 study, PFS2 is defined as the time from randomisation to second disease progression (assessment by imaging, CA-125[3] measurement, or by symptomatology) or death following first progression (PFS1).

In the SOLO1 study, the median PFS2 for the first data cut-off of 17 May 2018 was not reached in the intervention arm. For the control arm, the median PFS2 at this time is 41.9 months. The survival analysis shows a statistically significant difference between olaparib compared with placebo.

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

The morbidity component of disease progression of endpoint PFS2 was assessed by imaging techniques, laboratory parametric surveys (CA-125 measurement), or on the basis of symptoms (symptomatic progress). However, symptomatic progress was reported as the reason for diagnosis in only four patients (1.0%) with a PFS2 event. In addition, as already discussed for the endpoint PFS1, routine instrumental diagnostics and marker determination,

[3] Cancer antigen - 125

in particular determination of the CA-125 level, should not be performed in symptom-free patients in the present therapeutic indication. In consideration of the aspects listed, the endpoint PFS2 is not used for the benefit assessment.

Relapses

In the dossier, the pharmaceutical company describes endpoints of the complex "relapses" and, based on a sub-population of female patients, presents the following *post hoc* defined operationalisations:

- Relapse rate: Proportion of patients with new target/non-target lesions.
- Relapse-free survival (RFS): combined endpoint of time from randomisation to the occurrence of a new target lesion/non-target lesion or death of any cause.
- Time to relapse: operationalised as time from randomisation to the appearance of a new target/non-target lesion.

The evaluations are based on the PFS1 data of those patients who showed a complete response to the preceding platinum-based first-line chemotherapy when randomised (approx. 82% of the PFS population). For this sub-population, the pharmaceutical company defines each new target/non-target lesion detected in accordance with RECIST as a relapse. In doing so, it assumes a curative therapy approach and interprets the occurrence of a relapse as the failure of a healing attempt.

According to the generally recognised state of medical knowledge, the vast majority of patients in the present therapeutic indication are expected to have a relapse or progression in the further course of the disease. Even after complete clinical or pathologically complete response, several studies[4,5] show a high rate of relapse after platinum-containing first-line chemotherapy. The results of the SOLO1 study also show a high relapse rate of about 70% after 5 years of study duration in patients with a complete response to randomisation in the comparator arm. The estimates presented by clinical experts in the present written statement procedure also do not indicate that a curative therapy approach can generally be assumed in the present therapeutic indication.

Whether the use of olaparib in maintenance treatment could lead to a curative situation cannot yet be conclusively assessed because the results of the SOLO1 study are of little significance because of the relatively short observation period compared with the data cut-off available.

The results for the endpoints on the complex "relapses" are therefore not used in the present assessment.

Health status (EQ-5D visual analogue scale)

In order to assess the health status of the study patients, the pharmaceutical company presents responder analyses for the time to first deterioration by ≥ 7 points and by ≥ 10 points compared with baseline.

Instead of the responder analyses, the dossier evaluation of the IQWiG uses analyses of mean differences. The difference between the study arms is not statistically significant regarding mean difference.

[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.

The IQWiG classifies the study on which the derivation of the MID for the responder analyses is based (Pickard et al., 2007) as unsuitable to prove the validity of the MID. This is justified on one hand by the fact that the work mentioned does not contain a longitudinal study to determine the MID, which is assumed in the current scientific discussion on deriving a valid MID. In addition, the IQWiG does not consider the ECOG-PS and FACT-G anchors used in the study to be suitable for the derivation of MID.

In view of the fact that responder analyses based on a MID have general advantages for a clinical evaluation of effects compared with an analysis of standardised mean differences and taking into account that the validation study in question has already been used in earlier evaluations, the G-BA nevertheless uses the responder analyses in the present assessment to assess the effects on symptomatology.

There are no statistically significant differences in the time to first deterioration.

Overall, based on the endpoints used for assessment, neither advantages nor disadvantages of treatment with olaparib are shown with regard to morbidity.

Quality of life

In the SOLO1 study, health-related quality of life is recorded using the disease-specific questionnaire FACT-O. There is a statistically significant difference in the overall score for the mean change at month 24 to the disadvantage of olaparib. However, the 95% confidence interval of the standardised mean difference (Hedges' g) is not completely outside the irrelevance range of −0.2 to 0.2. It can therefore not be deduced that a relevant effect exists. An additional benefit of olaparib is therefore not proven.

Side effects

Adverse events (AE) in total

In the SOLO1 study, approx. 99% of patients in the intervention arm and approx. 92% of patients in the comparator arm experienced an adverse event. The results for the endpoint "total adverse events" are only presented on a supplementary basis.

Serious AE

In the SOLO1 study, approx. 21% of patients in the intervention arm and approx. 12% of patients in the comparator arm experienced a serious adverse event. The event time analysis shows no statistically significant difference.

Severe AE (CTCAE grade ≥ 3)

In the SOLO1 study, approx. 39% of patients in the intervention arm and approx. 19% of patients in the comparator arm experienced a severe adverse event (CTCAE grade ≥ 3). The event time analysis shows a statistically significant difference to the disadvantage of olaparib.

Therapy discontinuation because of AE

At the time of this data cut-off, approx. 12% of patients in the intervention arm and approx. 2% of patients in the comparator arm had discontinued treatment because of adverse events. Event time analysis shows a statistically significant difference between the treatment groups to the disadvantage of olaparib.

Specific AE

In the area of specific adverse events, there are statistically significant differences to the detriment of olaparib with regard to anaemia (PT, severe AE), taste disorder (PT, AE), dyspnoea (PT, AE), nausea (PT, AE), stomatitis (PT, AE), vomiting (PT, AE), muscle spasms (PT, AE), asthenia (PT, AE), and mucosa inflammation (PT, AE).

Overall, the results on adverse events show negative effects for olaparib compared with the monitoring wait-and-see approach with an increase in severe AE (CTCAE grade ≥ 3) and therapy discontinuation because of AE. In detail, the negative effects are also evident in the area of specific AE.

Overall assessment

For the benefit assessment olaparib as monotherapy for the treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) 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, results from the SOLO1 study on overall survival, morbidity, health-related quality of life, and side effects are available.

In the mortality endpoint category, there was no statistically significant difference between olaparib and the monitoring wait-and-see approach. An additional benefit of olaparib is thus not proven for overall survival. However, the data available on this endpoint are still not very significant (particularly because of the low number of events that have occurred to date) and can therefore not be conclusively assessed. The final data on overall survival from the current study is still pending.

Overall, based on the endpoints used for the assessment neither advantages nor disadvantages of treatment with olaparib are shown with regard to morbidity.

Regarding health-related quality of life, the overall score of the disease-specific questionnaire FACT-O shows a statistically significant difference to the disadvantage of olaparib. However, it cannot be deduced with sufficient certainty that this effect is clinically relevant.

In the endpoint category adverse events, negative effects for olaparib compared with the appropriate comparator therapy are shown by an increase in severe AE (CTCAE grade ≥ 3) and therapy discontinuation because of AE. In detail, the negative effects are also evident in the area of specific AE.

Overall, based on the data basis available, it is not possible to conclusively weigh the positive and negative effects of olaparib against the appropriate comparator therapy. For olaparib as monotherapy for the treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) 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, an additional benefit 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 has 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 this case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

The overall survival data from the SOLO1 study available for this assessment are inconclusive because of the still limited number of occurrences at the time of the data cut-off. The final analysis of overall survival from the current study is still pending.

In view of the fact that clinical data on overall survival relevant for the benefit assessment of the medicinal product are expected in the future, the G-BA considers it appropriate to limit the period of validity of the resolution until further scientific evidence on the additional benefit of olaparib is available. The limitation allows the expected final results from the SOLO1 study to be included in the benefit assessment of the medicinal product according to Section 35a SGB V.

For this purpose, the G-BA considers a limitation of the resolution until 1 April 2024 to be appropriate.

Conditions of the limitation:

For the renewed benefit assessment after the deadline, the dossier should include the results expected in 2024 from the final analysis on overall survival and other patient-relevant outcomes from the SOLO1 study used to demonstrate an additional benefit.

The G-BA is able, in principle, to revise the limitation if it has been presented with clear justification that it is insufficient or too long.

In accordance with Section 3, paragraph 1 number 5 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of olaparib shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline proving an additional benefit of olaparib in relation to the appropriate comparator therapy (Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, No. 5 VerfO). If the dossier is not submitted or submitted incompletely, the G-BA may come to the finding that an additional benefit is not proven.

The possibility that a benefit assessment for olaparib can be carried out at an earlier point in time for other reasons (*cf.* Chapter 5, Section 1, paragraph 2 VerfO) remains unaffected by this.

2.1.5 Summary of the assessment

The present assessment concerns the benefit assessment of a new therapeutic indication for the active ingredient olaparib:

“Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) 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”.

A monitoring wait-and-see approach was determined to be an appropriate comparator therapy.

The pharmaceutical company presents the results of the randomised, double-blind, placebo-controlled SOLO1 study for the benefit assessment. The placebo comparison carried out in this study sufficiently corresponds to the appropriate comparator therapy, a “monitoring wait-and-see approach”.

The data on overall survival are preliminary, and therefore no assessment of the effectiveness can as yet be drawn for the mortality endpoint category. Based on the available data, there is no statistically significant difference in overall survival between the study arms. Final results on the overall survival endpoint from the current study are pending.

Based on the endpoints used for the assessment neither advantages nor disadvantages of treatment with olaparib are shown with regard to morbidity.

For health-related quality of life, a statistically significant disadvantage of olaparib is shown in the overall FACT-O score, although it cannot be deduced that this is a relevant effect.

In the side effects endpoint category, there are statistically significant differences to the detriment of olaparib in severe AE (CTCAE grade ≥ 3), therapy discontinuation because of AE, and, in detail, in the area of specific AE.

In view of the current lack of significant data on overall survival, the results cannot be conclusively assessed. In conclusion, the additional benefit of olaparib is not proven.

The resolution is limited until 1 April 2024.

For the renewed benefit assessment after the deadline, the dossier should include the results expected in 2024 from the final analysis on overall survival and other patient-relevant outcomes from the SOLO1 study used to demonstrate an additional benefit.

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

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

The resolution will be based on the information from the dossier of the pharmaceutical company regarding the number of patients. Overall, it is assumed that this is an underestimate. In particular, the delimitation of the target population carried out by the pharmaceutical company on the basis of proportional values for BRCA mutation tests leads to a potential underestimation of the patient numbers. Furthermore, there is a tendency to underestimate the estimated incidence of ovarian, tubal, and peritoneal cancers as well as the number of patients who have progressed to an advanced stage in the current year. A derivation step to epithelial, invasive forms of ovarian cancer is also missing. There are also uncertainties regarding the operationalisation used by the pharmaceutical company to respond to platinum-based first-line chemotherapy.

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: 17 October 2019).

https://www.ema.europa.eu/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 cancer.

Before starting treatment with Lynparza for first-line maintenance treatment of high-grade epithelial ovarian cancer (EOC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC), mutations in the breast cancer susceptibility genes (BRCA) 1 or 2 that are harmful or suspected of being harmful to patients must have been confirmed in the germ line and/or tumour using a validated test 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: 15 December 2019).

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:

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 × daily	365	1	365
Appropriate comparator therapy				
Monitoring wait-and-see approach	not quantifiable			

Usage and consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Mean annual consumption by potency
Medicinal product to be assessed					
Olaparib	300 mg	600 mg	4 × 150 mg	365	1,460 × 150 mg
Appropriate comparator therapy					
Monitoring wait-and-see approach	not quantifiable				

Costs:

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

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy selling price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Olaparib	112 FCT	€ 6,730.08	€ 1.77	€ 381.08	€ 6,347.23
Appropriate comparator therapy					
Monitoring wait-and-see approach	not quantifiable				
Abbreviations: FCT = film-coated tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 December 2019

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 standard expenditure in the course of the treatment are not shown.

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

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 26 February 2019.

On 10 July 2019, 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 11 July 2019 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 11 October 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 15 October 2019. The deadline for submitting written statements was 5 November 2019.

The oral hearing was held on 26 November 2019.

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 were discussed at the session of the subcommittee on 7 January 2020, and the proposed resolution was approved.

At its session on 16 January 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	26 February 2019	Determination of the appropriate comparator therapy
Working group Section 35a	20 November 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	26 November 2019	Conduct of the oral hearing
Working group Section 35a	4 December 2019 18 December 2019	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	7 January 2020	Concluding consultation of the proposed resolution
Plenum	16 January 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 16 January 2020

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

Prof. Hecken