Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Olaparib (new therapeutic indication: breast cancer, HER2-, BRCA1/2-mutation, pretreated, high risk of recurrence, adjuvant treatment, monotherapy or combination with endocrine therapy)

of 16 February 2023

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The active ingredient olaparib (Lynparza) was listed for the first time on 1 June 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 2 August 2022, Lynparza received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 22 August 2022, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 of the 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 (breast cancer, HER2,-, BRCA1/2-mutation, pretreated, high risk of recurrence, adjuvant therapy, monotherapy or combination with endocrine therapy).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 December 2022 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

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

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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

2.1.1 Approved therapeutic indication of Olaparib (Lynparza) in accordance with the product information

Lynparza is indicated as monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.

Therapeutic indication of the resolution (resolution of 16.02.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with germline BRCA-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy; adjuvant therapy

Appropriate comparator therapy for olaparib as monotherapy or in combination with endocrine therapy:

- Monitoring wait-and-see approach

[1] General Methods, version 6.1 from 24.01.2022. 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 G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

on 1. In addition to olaparib, the active ingredients tamoxifen, anastrozole, exemestane, letrozole, leuprorelin, goserelin, triptorelin, cyclophosphamide, docetaxel, doxorubicin, epirubicin, fluorouracil, methotrexate, paclitaxel, vincristine and abemaciclib are approved in the present therapeutic indication.

Medicinal products with explicit marketing authorisation for HER2-positive breast cancer and for advanced, metastatic breast cancer were not considered.

on 2. Radiotherapy is generally considered as a non-medicinal treatment in the present therapeutic indication.

However, it is assumed that the patients have received prior adjuvant radiotherapy. An adjuvant radiotherapy is therefore not part of the appropriate comparator therapy.

on 3. In the therapeutic indication, the following resolutions from the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available:

- Abemaciclib (in combination with endocrine therapy): Resolution of 20 October 2022

In the therapeutic indication, the following resolutions or guidelines of the G-BA for medical or non-medicinal treatments are available:

Directive on Examination and Treatment Methods in Hospitals (Directive on Methods of Inpatient Treatment) - Methods excluded from provision at the expense of the statutory health insurance funds; entered into force on 20 March 2019:

- Proton therapy for breast cancer

Annex VI to Section K of the Pharmaceuticals Directive – Active ingredients that cannot be prescribed for off-label use:

- Gemcitabine in monotherapy for breast cancer in women

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a paragraph 7 SGB V.

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

For the adjuvant treatment of BRCA-mutated, HER2-negative breast cancer after completion of (neo)adjuvant chemotherapy, there are no recommendations in either national or international guidelines for further, regularly indicated specific therapy.

The active ingredient abemaciclib is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved (marketing authorisation on 01.04.2022). Based on the generally accepted state of medical knowledge, abemaciclib is not determined to be an appropriate comparator therapy for the present resolution.

In the reality of care, patients are regularly examined as part of after-care. Thus, for the present treatment setting according to the therapeutic indication, monitoring wait-and-see approach is determined as the appropriate comparator therapy.

The present therapeutic indication also includes patients with hormone receptor-positive breast cancer. Additional administration of endocrine therapy to these patients is assumed.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5, Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

There is an indication of a minor additional benefit of olaparib as monotherapy or in combination with endocrine therapy for the adjuvant treatment of adults with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.

Justification:

For the evidence of additional benefit, the pharmaceutical company submitted the results of the still ongoing, double-blind, randomised controlled trial OlympiA in the dossier, in which olaparib is compared with placebo.

Adults with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer were enrolled in the study. Initially, only patients with triple-negative breast cancer (TNBC) could be enrolled in the OlympiA study; the enrolment of patients with a positive hormone receptor status was permitted for protocol version 3.0 and above (21.10.2015). A prerequisite for enrolment was the completion of adequate breast and axilla surgery. Based on the specifications for adequate breast and axilla surgery, a curative treatment approach is assumed for the patients. Furthermore, patients had to have received at least 6 cycles of neoadjuvant or adjuvant chemotherapy with anthracyclines, taxanes or a combination of both as pretreatment. Pretreatment with a platinum substance as part of neoadjuvant or adjuvant chemotherapy was allowed.

A total of 1,836 patients were enrolled in the study, randomised in a 1:1 ratio and allocated to treatment with olaparib (N = 921) or placebo (N = 915). The treatment with olaparib in the intervention arm was carried out according to the requirements in the product information for maximum 12 months. A changeover to the treatment of the other study arm was not planned. In both treatment arms, hormone receptor-positive patients should receive adjuvant endocrine therapy according to local and/or international guidelines. The information in the OlympiA study report shows that about 90% of the patients with hormone receptor-positive breast cancer in the study received endocrine therapy.

In the context of (neo)adjuvant chemotherapy, treatment with platinum substances was carried out in 26.4% of the patients. Platinum substances are not approved for the (neo)adjuvant therapy of breast cancer. However, the therapy with platinum substances is partly presented in the guidelines. Furthermore, treatment with platinum substances took place prior to randomisation, and the additional stratification by this criterion means that there is a balanced distribution between the treatment arms. The facts therefore remain without consequence for the present assessment.

The study ongoing since 2014 is being conducted at 554 study sites in Asia, Australia, Europe, North America and South America. The primary endpoint of the study is invasive disease-free survival (iDFS). Patient-relevant secondary endpoints were collected in the categories of mortality, morbidity, health-related quality of life, and adverse events (AEs).

At the time of the benefit assessment, 2 data cut-offs were available:

- 1st data cut-off from 27.03.2020: planned interim analysis after 165 iDFS events in the first 900 patients enrolled
- 2nd data cut-off from 12.07.2021: planned final iDFS analysis after 330 iDFS events

For the present benefit assessment, the results of the 2nd data cut-off from 12 July 2021 are used.

Implementation of the appropriate comparator therapy

In the OlympiA study, targeted physical examinations were carried out on all patients during follow-up visits and clinical signs and symptoms were regularly recorded. However, the studies conducted in the placebo arm do not fully reflect the guideline recommendations for patients in the present treatment setting. Overall, however, the patients in the OlympiA study were examined closely and specifically to detect recurrences, so that the examination regime

overall is considered to be sufficient implementation of the appropriate comparator therapy of the monitoring wait-and-see approach.

Extent and probability of the additional benefit

Mortality

The overall survival was defined in the OlympiA study as the time from randomisation to death from any cause.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of olaparib versus the monitoring wait-and-see approach. The median survival time has not yet been reached in either treatment group.

Morbidity

Recurrences (recurrence rate and disease-free survival)

Patients in the present therapeutic indication are treated with a curative therapeutic approach. The failure of a curative therapeutic approach is fundamentally patient-relevant. The significance of the endpoints on recurrences depends on the extent to which the selected individual components are suitable for adequately reflecting the failure of potential cure by the present curative therapeutic approach.

In the present benefit assessment, recurrences are taken into account in the endpoint of recurrence rate as well as in the endpoint of disease-free survival. Both evaluations include the following events:

- ipsilateral invasive recurrence,
- locoregional invasive recurrence,
- distant recurrence,
- contralateral invasive breast cancer,
- secondary primary tumour (not breast cancer),
- ductal carcinoma in situ and
- death from any cause.

In the present therapeutic indication, this operationalisation is suitable to depict a failure of the potential cure by the curative therapeutic approach.

There is a statistically significant difference in the operationalisation as event rate as well as in the time-to-event analysis to the advantage of olaparib over monitoring wait-and-see approach.

At the present data cut-off, the median time to recurrence event has not been reached in either treatment group. The absolute difference in terms of recurrence rate is 8.0% (138 events out of 921 (15%) vs 210 events out of 915 (23%) patients). In the consideration of both endpoints, an overall relevant advantage of olaparib over monitoring wait-and-see approach is found with regard to the avoidance of recurrences.

Symptomatology (EORTC QLQ-C30 and FACIT-Fatigue)

In the OlympiA study, patient-reported symptomatology was collected using the EORTC QLQ-C30 and the FACIT-Fatigue.

EORTC QLQ-C30

For the endpoint of nausea and vomiting, there is a statistically significant difference to the disadvantage of olaparib over monitoring wait-and-see approach. The 95% confidence interval (CI) of the standardised mean difference (SMD) is completely outside the irrelevance range [-0.2; 0.2]. This is interpreted as a relevant effect.

For the endpoints of fatigue, loss of appetite and constipation, there was a statistically significant difference to the disadvantage of olaparib over monitoring wait-and-see approach. However, the respective 95% CIs of the SMD are not completely outside the irrelevance range [-0.2; 0.2]. Thus, it cannot be inferred, in each case, that the effect is relevant.

There was no statistically significant difference between the treatment arms for each of the endpoint's pain, dyspnoea, insomnia and diarrhoea.

FACIT fatigue

For the endpoint of fatigue, collected by the FACIT-Fatigue, there was a statistically significant difference to the disadvantage of olaparib over placebo. However, the 95% CI of the SMD is not completely outside the irrelevance range [-0.2; 0.2]. Thus, it cannot be inferred that the effect is relevant.

In summary, with regard to patient-reported symptomatology, there is only a disadvantage of olaparib over monitoring wait-and-see approach in the endpoint of nausea and vomiting. Uncertainties relevant to the assessment must be taken into account when interpreting this result, as a relevant percentage of patients were not included in the evaluation for the patient-reported endpoints.

In the overall assessment, therefore, no difference relevant to the assessment is found with regard to the symptomatology.

Quality of life

EORTC QLQ-C30

For health-related quality of life, the global health status scale shows a statistically significant difference to the disadvantage of olaparib over monitoring wait-and-see approach. However, the 95% CI of the SMD is not completely outside the irrelevance range [-0.2; 0.2]. Thus, it cannot be inferred that the effect is relevant.

There was no statistically significant difference between the treatment groups for each of the functional scales physical functioning, role functioning, cognitive functioning, emotional functioning and social functioning.

In summary, in the quality of life category, there are no advantages or disadvantages of olaparib over monitoring wait-and-see approach.

Side effects

Adverse events (AEs)

In the OlympiA study, an adverse event occurred in 91.8% of patients in the intervention arm and 83.8% thereof in the comparator arm. The results were only presented additionally.

Serious adverse events (SAE)

In the dossier, the pharmaceutical company submitted evaluations for the endpoint SAE, in which a relevant percentage of progression events from the system organ class of benign, malignant and unspecified neoplasms (including cysts and polyps) were included. This evaluation was not considered suitable by IQWiG in the dossier assessment because progression events from the system organ class of benign, malignant and unspecified neoplasms (including cysts and polyps) were already included in the morbidity category via recurrences and an additional consideration of the events would pose a risk of bias to the endpoint SAE to the advantage of olaparib.

In its written statement, the pharmaceutical company consequently submitted an evaluation for the endpoint SAE, in which the system organ class of benign, malignant and unspecified neoplasms (including cysts and polyps) was not taken into account. This evaluation is considered appropriate and is used for the present assessment. There is no statistically significant difference between the treatment arms here.

Severe adverse events (CTCAE grade ≥ 3) and discontinuation due to AEs

A statistically significant difference to the disadvantage of olaparib over the monitoring wait-and-see approach is observed for each of the endpoints severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs.

Specific adverse events

In detail, there is no statistically significant difference between the treatment arms for the specific AEs of MDS and AML (SMQ + PT list, AE) and pneumonitis (SMQ, AE). For the specific AEs of fatigue (PT, AE), gastrointestinal disorders (SOC, AE), dysgeusia (PT, AE), loss of appetite (PT, AE), anaemia (PT, SAE) and investigations (SOC, severe AE), there is a statistically significant difference to the disadvantage of olaparib over monitoring wait-and-see approach.

In summary, due to the disadvantages in the endpoints of severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs, a relevant overall disadvantage in side effects can be identified for treatment with olaparib compared to the monitoring wait-and-see approach. With regard to specific adverse events, there are detailed disadvantages of olaparib over monitoring wait-and-see approach.

<u>Overall assessment</u>

For the benefit assessment of olaparib as monotherapy or in combination with endocrine therapy for the adjuvant treatment of germline BRCA-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy, results from the still ongoing, double-blind, randomised controlled trial OlympiA are available for the endpoint categories of mortality, morbidity, health-related quality of life and side effects.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of olaparib versus the monitoring wait-and-see approach. The median survival time has not yet been reached in either treatment group.

In the morbidity category, a statistically significant difference in favour of olaparib compared to monitoring wait-and-see approach was shown with regard to recurrences, operationalised as recurrence rate and disease-free survival. The avoidance of recurrences is an essential

therapeutic goal in the present curative treatment setting. In this respect, there is a relevant advantage of olaparib over monitoring wait-and-see approach.

With regard to the patient-reported symptomatology, there are no differences relevant to the assessment.

In the quality of life category, there were no advantages or disadvantages of olaparib over monitoring wait-and-see approach.

In terms of side effects, there are statistically significant disadvantages of olaparib over monitoring wait-and-see approach in the endpoints of severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs, as well as in detail for specific adverse events.

In the overall analysis, the relevant advantages with regard to the improvement in overall survival and the avoidance of recurrences are offset by the disadvantages in terms of side effects. The disadvantages in terms of side effects are weighted against the background of the present curative therapy claim. Overall, the advantages outweigh the disadvantages, thus confirming the presence of an additional benefit. The present effect with regard to the avoidance of recurrences particularly serves as a guidance for the assessment of the extent of the additional benefit. Taking into account the recurrence rates in both treatment groups and the absolute difference in the recurrence rates, the G-BA concludes that in the overall assessment in the present case, the extent of a considerable additional benefit cannot be assumed with sufficient certainty.

Thus, olaparib is found to have a minor additional benefit compared to the monitoring wait-and-see approach.

Reliability of data (probability of additional benefit)

The underlying OlympiA study is a double-blind, randomised controlled trial.

The risk of bias across endpoints for the OlympiA study is rated as low at study level.

The risk of bias in the results for the endpoints of overall survival and recurrences, as well as for all endpoints in the category of side effects, is rated as low.

In the overall analysis, the reliability of data for the additional benefit determined is classified in the category "indication".

2.1.4 Summary of the assessment

This assessment is a benefit assessment of a new therapeutic indication for the active ingredient olaparib as monotherapy or in combination with endocrine therapy for the adjuvant treatment of adults with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.

The "monitoring wait-and-see approach" was determined as the appropriate comparator therapy.

For the proof of an additional benefit, results from the double-blind, randomised controlled OlympiA study were presented for the endpoint categories mortality, morbidity, quality of life and side effects.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of olaparib versus the monitoring wait-and-see approach.

In the morbidity category, there were statistically significantly fewer recurrences under treatment with olaparib compared to the monitoring wait-and-see approach. In the present curative treatment setting, the avoidance of recurrences is an essential therapeutic goal. The extent to which recurrences are avoided is assessed as a relevant advantage.

With regard to patient-reported symptomatology and health-related quality of life, there were no differences relevant to the assessment.

In terms of side effects, there are statistically significant disadvantages of olaparib compared to monitoring wait-and-see approach in the endpoints of severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs, as well as in detail for specific adverse events.

In the overall analysis, the relevant advantages with regard to the improvement in overall survival and the avoidance of recurrences are offset by the disadvantages in terms of side effects. The disadvantages in terms of side effects are weighted against the background of the present curative therapy claim. Overall, the advantages outweigh the disadvantages, thus confirming the presence of an additional benefit. The present effect with regard to the avoidance of recurrences particularly serves as a guidance for the assessment of the extent of the additional benefit. Taking into account the recurrence rates in both treatment groups and the absolute difference in the recurrence rates, the G-BA concludes that in the overall assessment in the present case, the extent of a considerable additional benefit cannot be assumed with sufficient certainty.

Thus, olaparib is found to have a minor additional benefit compared to the monitoring wait-and-see approach.

The reliability of data is classified in the "indication" category, in particular due to the low risk of bias at study level and for the endpoints that are relevant for the assessment decision.

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

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

The resolution is based on the information from the dossier of the pharmaceutical company. However, the pharmaceutical company's approach is in part mathematically incomprehensible and fraught with uncertainties. The methodological procedure leads to both overestimates and underestimates in specific derivation steps, as well as to uncertainty. In particular, the implementation of the criteria of indication for chemotherapy and high risk of recurrence is uncertain. There are also uncertainties due to an unclear number of unconsidered patients with, for example, new local recurrence in the year under review, an unclear number of considered patients in stage IIIC outside the therapeutic indication and in the percentage values for a high risk of recurrence and for the presence of a BRCA1/2 mutation.

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: 31 January 2023):

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

Treatment with olaparib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology who are experienced in the treatment of patients with breast cancer, as well as specialists in obstetrics and gynaecology, and other specialists participating in the Oncology Agreement.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 February 2023).

The use of olaparib is limited to 1 year.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

The (daily) doses recommended in the product information or in the labelled publications were used as the basis for calculation.

Treatment period:

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 monotherapy				
Olaparib	Continuously, 2 x daily	365	1	365
Olaparib in combination with endocrine therapy				
Olaparib	Continuously, 2 x daily	365	1	365
Aromatase inhibitor[2] or anti-estrogen[3]				
Anastrozole	Continuously, 1 x daily	365	1	365

[2] Anastrozole or letrozole
[3] Tamoxifen

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Letrozole	Continuously, 1 x daily	365	1	365
Tamoxifen	Continuously, 1 x daily	365	1	365
+ GnRH agonist, if necessary[4]				
Leuprorelin	Continuously, 1 x every 3 months	4	1	4
Goserelin	Continuously, 1 x every 28 days	13	1	13
Appropriate comparator therapy				
Monitoring wait-and-see approach	Incalculable			

Consumption:

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Olaparib monotherapy					
Olaparib	300 mg	600 mg	6 x 100 mg	365	2,190 x 100 mg
Olaparib in combination with endocrine therapy					
Olaparib	300 mg	600 mg	6 x 100 mg	365	2,190 x 100 mg
Aromatase inhibitor[2] *or anti-estrogen*[3]					
Anastrozole	1 mg	1 mg	1 x 1 mg	365	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365	365 x 2.5 mg
Tamoxifen	20 mg	20 mg	1 x 20 mg	365	365 x 20 mg

[4] Leuprorelin or goserelin; in premenopausal patients, cessation of ovarian function with a GnRH analogue is generally indicated during treatment with tamoxifen

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
+ GnRH agonist, if necessary[4]					
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4	4 x 11.25 mg
Goserelin	3.6 mg	3.6 mg	1 x 3.6 mg	13	13 x 3.6 mg
Appropriate comparator therapy					
Monitoring wait-and-see approach	Incalculable				

Costs:

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

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Olaparib 100 mg	112 FCT	€ 3,316.30	€ 2.00	€ 319.04	€ 2,995.26
Anastrozole 1 mg[5]	120 FCT	€ 65.06	€ 2.00	€ 4.25	€ 58.81
Goserelin 3.6 mg	3 IMP	€ 547.76	€ 2.00	€ 50.92	€ 494.84
Letrozole 2.5 mg[5]	120 FCT	€ 61.64	€ 2.00	€ 3.98	€ 55.66
Leuprorelin 11.25 mg	2 SRM	€ 981.40	€ 2.00	€ 92.08	€ 887.32
Tamoxifen 20 mg[5]	100 FCT	€ 22.43	€ 2.00	€ 0.88	€ 19.55
Appropriate comparator therapy					
Monitoring wait-and-see approach	Incalculable				
Abbreviations: FCT = film-coated tablets, IMP = implant, SRM = sustained-release microcapsules and suspension agents					

LAUER-TAXE® last revised: 1 February 2023

[5] Fixed reimbursement rate

Costs for additionally required SHI services:

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

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

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

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with pembrolizumab

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

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

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 12 October 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 22 August 2022, the pharmaceutical company submitted a dossier for the benefit assessment of olaparib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2, sentence 1 VerfO.

By letter dated 25 August 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products

with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient olaparib.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 November 2022, and the written statement procedure was initiated with publication on the G-BA website on 1 December 2022. The deadline for submitting written statements was 22 December 2022.

The oral hearing was held on 9 January 2023.

By letter dated 10 January 2023, 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 26 January 2023.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 7 February 2023, and the proposed resolution was approved.

At its session on 16 February 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	12 October 2021	Determination of the appropriate comparator therapy
Working group Section 35a	3 January 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	9 January 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	17 January 2023; 31 January 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	7 February 2023	Concluding discussion of the draft resolution
Plenum	16 February 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 February 2023

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

Prof. Hecken