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: Breast Cancer; HER2 negative)

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

The active ingredient olaparib 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 8 April 2019, olaparib received the marketing authorisation for a new therapeutic indication classified as a major variation of Type 2 according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 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 December 2008, p. 7).

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 (HER2-negative, locally advanced, or metastatic breast cancer) 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, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of 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 treatment of adult patients with germline BRCA1/2 mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments.

Patients with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy for olaparib as monotherapy was determined as follows:

Adult patients with HER2-negative, locally advanced or metastatic breast cancer with BRCA1/2 mutations in the germ line; after prior therapy with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting or ineligible for these treatments

capecitabine or vinorelbine or eribulin or possibly an anthracycline- or taxane-containing therapy

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.

[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.

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.

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

On 1. In addition to olaparib, atezolizumab, bevacizumab, capecitabine, cyclophosphamide, docetaxel, doxorubicin, liposomal doxorubicin, epirubicin, eribulin, 5-fluorouracil, gemcitabine, ifosfamide, methotrexate, mitomycin, mitoxantrone, paclitaxel, nab-paclitaxel, vinblastine, vincristine, vindesine, and vinorelbine have been approved for the treatment of HER2-negative, locally advanced or metastatic breast cancer. Medicinal products with explicit marketing authorisation for the endocrine therapy of breast cancer were not included.

On 2. Non-medicinal treatment is not considered.

On 3. The following resolutions and guidelines of the G-BA have been issued for medicinal therapies in the present therapeutic indication:

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

Eribulin: Resolution of 22 January 2015

Guidelines:

Annex VI to Section K of the Pharmaceuticals Directive (Last revised: 17 October 2019)

Active ingredients that are not prescribable in off-label use:

Gemcitabine in monotherapy for female breast cancer

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

In determining the appropriate comparator therapy, it was assumed that endocrine therapy alone is no longer indicated for the patients. Furthermore, it was assumed that the patients usually received taxane- and/or anthracycline-based chemotherapy as part of the previous chemotherapy.

According to guideline recommendations, additional cytotoxic chemotherapy is the standard of care for patients with HER2-negative metastatic breast cancer who have undergone previous chemotherapeutic treatment for disease progression or relapse. Primarily monotherapies are recommended; only in cases of severe symptoms, rapid tumour growth, and aggressive tumour behaviour is polychemotherapy indicated.

If there is an indication for re-therapy with anthracyclines or taxanes or if a patient has not yet received a therapy containing anthracyclines and/or taxanes, representatives of these groups of active ingredients may be considered as a therapeutic option in the planned therapeutic indication because of their high significance in the treatment of breast cancer.

Capecitabine, vinorelbine, and eribulin are approved for use as monotherapy in the planned therapeutic indication apart from the active ingredients primarily named in various guidelines in addition to taxanes and anthracyclines.

For eribulin used to treat patients who have experienced further progression after at least one chemotherapy for advanced breast cancer, the G-BA has found a hint for a

considerable additional benefit compared with capecitabine or vinorelbine monotherapy for patients who can no longer be treated with taxanes or anthracyclines (resolution of 22 January 2015). Because of the low reliability of data and the restriction of the additional benefit to part of the approved therapeutic indication, eribulin is considered an equally appropriate therapeutic option alongside capecitabine and vinorelbine. The active ingredient atezolizumab is approved in combination with nab-paclitaxel for the treatment of locally advanced or metastatic triple-negative breast cancer (PD-L1 expression ≥ 1%) and is currently being subjected to a benefit assessment procedure in parallel to the present assessment.

In summary, "capecitabine or vinorelbine or eribulin or possibly an anthracycline- or taxane-containing therapy" was therefore determined as the appropriate comparator therapy for olaparib as monotherapy in the present 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 as monotherapy is assessed as follows:

Adult patients with HER2-negative, locally advanced or metastatic breast cancer with BRCA1/2 mutations in the germ line; after prior therapy with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting or ineligible for these treatments

For the treatment of adult patients with HER2-negative, locally advanced or metastatic breast cancer with BRCA1/2 mutations in the germ line previously treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting or who were ineligible for these treatments, there is a hint for a minor additional benefit.

Justification:

To demonstrate an additional benefit of olaparib for the treatment of HER2-negative, locally advanced or metastasised breast cancer, the pharmaceutical company has presented the results of the OlympiAD study.

OlympiAD is a multi-centric, open, randomised controlled trial comparing olaparib with chemotherapy according to the doctor's instructions using capecitabine or vinorelbine or eribulin. The ongoing global study, which started in May 2014, includes adult female and male patients with HER2-negative metastatic breast cancer with BRCA1/2 mutation in the germ line and an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 or 1. Patients had to have been pre-treated with an anthracycline and taxane in the (neo-)adjuvant or metastatic situation except in the presence of a contraindication. HR-positive patients also had to have received at least one endocrine therapy in the adjuvant or metastatic situation and underwent disease progression, or they had to have been ineligible for endocrine therapy. For the metastatic stage of the disease, a maximum of two previous chemotherapy lines were allowed. Patients with previous platinum-based chemotherapy for advanced breast cancer were included provided that no disease progression had occurred during platinum-based chemotherapy.

The 302 patients included were randomised 2:1 in the olaparib arm (N = 205) and in the arm with chemotherapy according to the doctor's instructions (capecitabine or vinorelbine or eribulin) (N = 97). The individual therapy was selected before randomisation. The patients were stratified according to prior chemotherapy in the metastatic stage (yes vs no),

oestrogen and/or progesterone receptor status (ER and/or PgR positive vs ER and PgR negative), and prior platinum-based chemotherapy of breast cancer (yes vs no).

Treatment with the study medication was continued until disease progression or discontinuation for other reasons (e.g. because of AE or patient decision). However, patients were also able to continue treatment despite disease progression if the investigator considered that the patients had a clinical benefit. The follow-up therapies after discontinuation of the study medication were not specified in the study protocol. A change of patients from the control arm to the intervention arm was not planned in the OlympiAD study.

OlympiAD is conducted in 125 study centres in Asia, Europe, and North and South America.

Four data cut-offs have taken place so far: first, the a priori planned primary analysis for the endpoint progression-free survival (PFS) (1st data cut-off) and the planned final assessment of the study (2nd data cut-off). second, two further post hoc planned data cut-offs from the extension phase of the study have taken place; these are not based on the ITT population. For the present benefit assessment, the 2nd data cut-off of 25 September 2017 is used.

Extent and probability of the additional benefit

Mortality

In the OlympiAD study, overall survival was defined as the time between randomisation and death regardless of the underlying cause of death.

For the overall survival endpoint, there was no statistically significant difference between treatment arms in the overall study population.

There was an effect modification by the feature “Previous chemotherapy of metastatic breast cancer” for overall survival. There was a statistically significant effect in favour of olaparib for patients without previous chemotherapy for metastatic breast cancer (HR: 0.51 [95% CI: 0.29; 0.90]; p = 0.013). However, for patients with previous chemotherapy for metastatic breast cancer, there was no significant difference between the treatment groups.
When interpreting this result, relevant uncertainties resulting from the small number of patients in the respective sub-groups should be taken into account.

The effect modification by the feature “Previous chemotherapy of metastatic breast cancer” is a relevant result in the context of the benefit assessment. However, the existing data basis is not sufficient to derive separate statements on additional benefit with the necessary certainty. As a result, no additional benefit is identified for the overall survival endpoint.

Morbidity

Progression-free survival (PFS)

In the OlympiAD study, progression-free survival was the primary endpoint and was defined as the time between randomisation and disease progression (determined by a central blinded independent radiological committee (BICR) using RECIST criteria version 1.1) or death regardless of the underlying cause.

In the intervention arm, there was a statistically significant increase in median PFS of 2.8 months compared with the control arm (median of 7.0 vs 4.2 months; HR: 0.58 [95% CI: 0.43; 0.80]; p = 0.0009).

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the present study, the endpoint component “mortality” was collected as an independent endpoint via the endpoint overall survival. The morbidity component was not assessed on the basis of symptoms but rather exclusively using imaging procedures (radiologically determined disease progression according to the RECIST criteria). Taking the aforementioned factors into consideration, there are differing opinions within the G-BA

regarding the relevance for patients of the PFS endpoint. The overall statement on the extent of the additional benefit remains unaffected.

Symptomatology

In the OlympiAD study, the symptomatology was measured using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30.

The survey was conducted every 6 weeks during treatment until disease progression and 30 days after the end of treatment.

In addition to evaluations of the time until the confirmed clinically relevant deterioration (both without and with consideration of death as an event), evaluations of the time until the confirmed clinically relevant improvement of the symptomatology and continuous analyses were presented by the pharmaceutical company.

Given the responder analyses presented, the evaluation of the time to clinically relevant deterioration (increase of the score by at least 10 points compared with baseline), which was confirmed in the following data collection without considering death as an event, is regarded as suitable in principle.

With regard to this evaluation, the dossier evaluation of the IQWiG criticised the lack of information on the proportional values of patients censored on day 1. Within the framework of the written statement procedure on the present benefit assessment, the pharmaceutical company submitted additional information in this regard. Because these show that the proportion of patients not included in the evaluations differs to a relevant extent (difference of more than 15 percentage points) between the treatment groups in almost all symptom scales, the certainty of results of the evaluations is to be regarded as insufficient. As a result, the responder analyses are not used in the present assessment.

With respect to the continuous analyses presented, it should also be noted that the proportion of patients not included in the evaluations differs to a relevant extent (difference of more than 15 percentage points) between the treatment groups. The continuous analyses are therefore not used in the present assessment.

There is thus no usable data on symptomatology.

Quality of life

In the OlympiAD study, the functional scales of the disease-specific questionnaire EORTC QLQ-C30 were used to assess the health-related quality of life.

The survey was conducted every 6 weeks during treatment until disease progression and 30 days after the end of treatment.

For the functional scales of EORTC QLQ-C30, the pharmaceutical company used an analysis strategy comparable to the evaluation of the symptomatology and submitted corresponding information on the proportion of patients censored on day 1 in the written statement procedure as already described for the symptom scales (morbidity).

Because the proportion of patients not included in the evaluations differs to a relevant extent (difference of more than 15 percentage points) between the treatment groups in almost all scales of the responder analyses for the function scales, the certainty of results of the evaluations is to be regarded as insufficient. As a result, the responder analyses are not used in the present assessment. This applies analogously to the corresponding continuous analyses.

There are therefore no usable data on health-related quality of life.

Side effects

Adverse events (AE)

All endpoints in the side effects category were collected up to 30 days after the last dose of the study medication.

In the OlympiAD study, 97.6% of the patients in the intervention arm and 95.6% in the comparator arm experienced an adverse event.

Serious adverse events (SAE)

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

Severe AE (CTCAE grade 3 or 4)

A statistically significant difference to the advantage of olaparib was found with regard to severe adverse events with CTCAE grade 3 or 4.

Discontinuation because of AE

For the endpoint “therapy discontinuation because of an AE”, there was a statistically significant difference to the advantage of olaparib.

Specific AE

Specific AE were selected by the IQWiG using events based on frequency and differences between treatment arms and taking into account patient relevance.
There were statistically significant benefits for olaparib in terms of the specific AE hand-foot syndrome, alopecia, and general disorders and administration site conditions as well as the specific severe AE (CTCAE grade 3 or 4) neutropoenia and vascular disease.

In contrast, olaparib showed statistically significant disadvantages with regard to the specific AE nausea and the specific severe AE (CTCAE grade 3 or 4) anaemia. In the overall consideration of the endpoints on specific AE, the positive effects of treatment with olaparib predominate.

In the side effects category, an overall advantage of olaparib compared with capecitabine, vinorelbine, or eribulin can thus be observed.

Overall assessment

For the assessment of the additional benefit of olaparib, results from the open, randomised, controlled OlympiAD study in comparison to capecitabine, vinorelbine, or eribulin on mortality (overall survival), morbidity, quality of life and side effects are available.

In the endpoint category mortality, the results available for the overall survival endpoint do not show a statistically significant effect in relation to the total population of the study.
No additional benefit is identified for the overall survival endpoint.

No usable data are available for the endpoints of the morbidity (symptomatology) and health-related quality of life categories because the certainty of results of the evaluations presented is to be regarded as insufficient against the background of the relevant differences in the proportion of patients not included in the treatment groups.

In terms of side effects, with respect to the endpoints severe adverse events (CTCAE grade 3 or 4) and discontinuation because of AE, advantages of olaparib compared with capecitabine, vinorelbine, or eribulin are observed. There is no difference for the endpoint serious AE. With respect to specific AE, the positive effects of olaparib predominate. In the

side effects category, an overall advantage of olaparib compared with capecitabine, vinorelbine, or eribulin can thus be observed.

Overall, based on the advantages in the endpoint category side effects, the G-BA determined a minor additional benefit for olaparib compared with capecitabine, vinorelbine, or eribulin.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of an open, randomised controlled trial. The cross-endpoint risk of bias is considered low for the study.

The endpoint specific risk of bias for the overall survival endpoint is also considered low.

Because of the open design of the OlympiAD study, a high risk of bias can largely be assumed in the side effects category.
Furthermore, there are no usable data for the morbidity and health-related quality of life endpoint categories.

For these reasons, the reliability of data for the additional benefit determined is considered as a hint.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of a new therapeutic indication for the active ingredient olaparib. The therapeutic indication assessed here is as follows: “Lynparza is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2 mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy”.

The appropriate comparator therapy was determined by the G-BA as follows:

capecitabine or vinorelbine or eribulin or possibly an anthracycline- or taxane-containing therapy

The pharmaceutical company presents the results from the open, randomised, controlled OlympiAD study comparing olaparib with chemotherapy according to the doctor’s instructions using capecitabine or vinorelbine or eribulin. The OlympiaAD study included patients with HER2-negative metastatic breast cancer with BRCA1/2 mutation in the germ line who were pre-treated with an anthracycline and taxane in the (neo-)adjuvant or metastatic situation except in the presence of a contraindication.

In the endpoint category mortality, for the endpoint overall survival, there was no statistically significant difference between treatment groups.

No usable data were available for the endpoints of the morbidity (symptomatology) and health-related quality of life categories.

In terms of side effects, with respect to the endpoints severe adverse events (CTCAE grade 3 or 4) and discontinuation because of AE, advantages of olaparib compared with capecitabine, vinorelbine, or eribulin were observed. There was no difference for the endpoint serious AE. With respect to specific AE, the positive effects of olaparib predominated. In the side effects category, an overall advantage of olaparib compared with capecitabine, vinorelbine, or eribulin was thus observed.
Overall, based on the advantages in the endpoint category side effects, the G-BA determined a minor additional benefit for olaparib compared with capecitabine, vinorelbine, or eribulin.

Against the background that, because the open design of the OlympiAD study, a high risk of bias can largely be assumed in the adverse events category and that no usable data are available for the morbidity and health-related quality of life endpoint categories, only a hint for an additional benefit can be derived with regard to the reliability of data.

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

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

The G-BA bases its resolution on the information from the dossier of the pharmaceutical company. It should be noted that the patient numbers presented are a clear underestimate. This is partly because on one hand, the proportion of patients from Stage IIIC onwards was estimated to be too low. On the other hand, patients with locally advanced breast cancer in Stage IIC or lower were not included. Furthermore, patients whose breast cancer was diagnosed in advanced or metastatic stage before 2015 or who were not eligible for treatment with an anthracycline and a taxane were not included. There is also an uncertainty for the range of proportional values with BRCA1/2 mutation.
The existing uncertainties regarding the data on the number of patients was not sufficiently eliminated by the statements of the pharmaceutical company even in the course of the written statement procedure on the present benefit assessment.

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: 11 September 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 locally advanced or metastatic breast cancer.

Before initiating Lynparza therapy in patients with breast cancer susceptibility gene (gBRCA1/2)-mutated, human epidermal growth factor receptor 2 (HER2)-negative, metastatic breast cancer, a damaging or suspected damaging gBRCA1/2 mutation must be confirmed in the germ line. The gBRCA1/2 mutation status should be detected by an experienced laboratory using a validated test method. Data for the clinical validation of a BRCA1/2 test in tumour tissue are currently not available for breast cancer.

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 November 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.

For doxorubicin and epirubicin, the cumulative total dose was considered (450–550 mg/m^2 for doxorubicin and 900–1,000 mg/m^2 for epirubicin, respectively). For doxorubicin and epirubicin there is product information with different dosage recommendations (doxorubicin:

50–80 mg/m² and 60–75 mg/m²; epirubicin: 75–90 mg/m² and 60–90 mg/m². The dosage recommendations with the largest range were used for the cost calculation: doxorubicin 50–80 mg/m² and epirubicin: 60–90 mg/m².

For dosages depending on body surface area (BSA), the average body measurements of adult females were used as a basis (average body size: 1.66 m, average body weight: 68.7 kg). From this, a body surface area of 1.76 m² is calculated (calculation according to Du Bois 1916)[2]

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				
Capecitabine	2 × daily on day 1–14 of a 21-day cycle	17	14	238
Vinorelbine	1 × per week	52	1	52
Eribulin	On Day 1 and 8 of a 21-day cycle	17	2	34
an anthracycline- or taxane-containing therapy				
Docetaxel	1 × every 3 weeks	17	1	17
Doxorubicin	1 × every 3 weeks	5–11[3]	1	5–11
Doxorubicin, pegylated	1 × every 4 weeks	13	1	13
Epirubicin	1 × every 3	10–16[4]	1	10–16

[2] German Federal Office For Statistics, Wiesbaden 2018: https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Gesundheitszustand-Relevantes-Verhalten/Publikationen/Downloads-Gesundheitszustand/koerpermasse-5239003179004.pdf?__blob=publicationFile
[3] Based on the total cumulative dose of maximum 450–550 mg/m².
[4] Based on the total cumulative dose of maximum 900–1,000 mg/m².

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
	weeks			
Paclitaxel	1 × every 3 weeks	17	1	17
nab-paclitaxel	1 × every 3 weeks	17	1	17

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					
Capecitabine	2,150 mg[5]	4,300 mg	8 × 500 mg + 2 × 150 mg	238	1,904 × 500 mg + 476 × 150 mg
Vinorelbine	25 mg/m² = 44 mg – 30 mg/m² = 52.8 mg	44 mg – 52.8 mg	1 × 50 mg – 1 × 50 mg + 1 × 10 mg	52	52 × 50 mg – 52 × 50 mg + 52 × 10 mg
Eribulin	1.23 mg/m² = 2.16 mg	2.16 mg	3 × 0.88 mg	34	102 × 0.88 mg
Anthracycline- or taxane-containing therapy					
Docetaxel	100	176 mg	1 × 160 mg +	17	17 × 160

[5] Product information for capecitabine (Xeloda®): Standard dose for BSA 1.67–1.78: 2,150 mg.

Designation of the therapy	Dosage/ application	Dosage/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Mean annual consumption by potency
	mg/m² = 176 mg		1 × 20 mg		mg + 17 × 20 mg
Doxorubicin	80 mg/m² = 140.8 mg	140.8 mg	1 × 150 mg	5 –	5 × 150 mg
	50 mg/m² = 88 mg –	88 mg–	1 × 100 mg	11	11 × 100 mg
Pegylated liposomal doxorubicin (PLD)	50 mg/m² = 88 mg	88 mg	2 × 20 mg + 1 × 50 mg	13	26 × 20 mg + 13 × 20 mg
Epirubicin	90 mg/m² = 158.4 mg –	158.4 mg	1 × 150 mg + 1 × 10 mg	10 –	10 × 150 mg + 10 × 10 mg
	60 mg/m² = 105.6 mg –	105.6 mg	1 × 100 mg + 1 × 10 mg	16	16 × 100 mg + 16 × 10 mg
Paclitaxel	175 mg/m² = 308 mg	308 mg	1 × 300 mg + 1 × 30 mg	17	17 × 300 mg + 17 × 30 mg
nab-paclitaxel	260 mg/m² = 457.6 mg	457.6 mg	5 × 100 mg	17	85 × 100 mg

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					
Capecitabine 500 mg[6]	120 FCT	€ 151.51	€ 1.77	€ 11.12	€ 138.62
Capecitabine 150 mg[6]	120 FCT	€ 53.81	€ 1.77	€ 3.39	€ 48.65
Docetaxel 160 mg	1 IFC	€ 1,397.30	€ 1.77	€ 175.44	€ 1,220.09
Docetaxel 20 mg	1 IFC	€ 172.35	€ 1.77	€ 7.66	€ 162.92
Doxorubicin 100 mg[6]	1 IFC	€ 285.46	€ 1.77	€ 0.00	€ 283.69
Doxorubicin 150 mg[6]	1 SFI	€ 418.02	€ 1.77	€ 0.00	€ 416.25
Pegylated liposomal doxorubicin (PLD) 20 mg	1 IFC	€ 762.00	€ 1.77	€ 41.58	€ 718.65
Pegylated liposomal doxorubicin (PLD) 50 mg	1 IFC	€ 1,877.59	€ 1.77	€ 103.96	€ 1,771.86
Eribulin 0.88 mg	6 SFI	€ 2,429.63	€ 1.77	€ 135.48	€ 2,292.38
Epirubicin 100 mg	1 SFI	€ 300.09	€ 1.77	€ 13.72	€ 284.60
Epirubicin 10 mg	1 SFI	€ 39.17	€ 1.77	€ 1.34	€ 36.06
Epirubicin 150 mg	1 SFI	€ 445.06	€ 1.77	€ 20.60	€ 422.69
Epirubicin 10 mg	1 SFI	€ 39.12	€ 1.77	€ 1.34	€ 36.01
Paclitaxel 300 mg	1 IFC	€ 1,045.26	€ 1.77	€ 49.08	€ 994.41
Paclitaxel 30 mg	1 IFC	€ 115.45	€ 1.77	€ 4.96	€ 108.72
nab-paclitaxel 100 mg	1 PIS	€ 429.03	€ 1.77	€ 52.91	€ 374.35
Vinorelbine 50 mg	10 IFC	€ 1,424.23	€ 1.77	€ 67.07	€ 1,355.39
Vinorelbine 10 mg	10 IFC	€ 293.68	€ 1.77	€ 13.42	€ 278.49
Abbreviations: FCT = film-coated tablets; IFC = concentrate for the preparation of an infusion solution; SFI = solution for injection; PIS = powder for the preparation of an infusion solution					

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

[6] 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 standard expenditure in the course of the treatment are not shown.

Cost per package	Costs after deduction of statutory rebates[7]	Cost per service[8]	Treatment days per year	Costs per patient per year
Paclitaxel				
Pre-medication: Dexamethasone 2 × 20 mg/day, oral				
20 × 20 mg: € 53.75 (FB)	€ 51.98 (€ 1.77; €0.00)	€ 5.20	17	€ 88.37
Antihistamine: Dimetindene 1 mg per 10 kg BW, i.v.				
5 × 4 mg: € 18.56	€ 14.82 (€ 1.77; € 1.97)	€ 5.93[9]	17	€ 100.78
Ranitidine: 50 mg/day, i.v.				
5 × 50 mg: € 15.02	€ 13.06 (€1.77; € 0.19)	€ 2.61	17	€ 44.40

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy retail price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.
According to the special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: arbitral award to determine the mg prices for parenteral preparations from proprietary medicinal products in oncology in the Hilfstaxe according to Section 129, paragraph 5c, sentences 2–5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic drugs of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. These additional costs are not added to the pharmacy retail price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for production and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

7 Section 130 SGB V and Section 130a SGB V
8 Proportionate costs of costs per package for consumption per treatment day
9 For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis (average height: 1.66 m, average body weight: 68.7 kg). Source: German Federal Office For Statistics, Wiesbaden 2018: https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

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 9 January 2018.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products redefined the appropriate comparator therapy at its session on 2 April 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.

By letter dated 26 November 2019, 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 December 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	9 January 2018	Determination of the appropriate comparator therapy
Subcommittee Medicinal	2 April 2019	Redefinition of the appropriate comparator therapy

Products		
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, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	3 December 2019 17 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