Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL):

Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V

Olaparib (new therapeutic indication: Prostate cancer, BRCA1/2-mutations, progression after hormonal treatment)

of 3 June 2021

Contents

1. Legal basis

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

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

2. Key points of the resolution

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

On 3 November 2020, olaparib received marketing authorisation for a new therapeutic indication to be classified as a major type 2 amendment as defined according to Annex 2 number 2 letter a) to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of amendments to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 30 November 2020, i.e. at the latest within four weeks after the disclosure, the pharmaceutical company on the marketing authorisation of a new area of application, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in

conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient olaparib with the new therapeutic indication (Prostate cancer, BRCA1/2-mutations, progression after hormonal treatment).

The G-BA commissioned IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 March 2021 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. An oral hearing was also held.

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

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

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

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

Lynparza is indicated as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior treatment that included a new hormonal agent.

Therapeutic indication of the resolution (resolution of 3/6/2021):

see approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with metastatic castration-resistant prostate cancer (mCRPC); BRCA1/2-mutated (germline and/or somatic); progressive disease after previous treatment with abiraterone and/or enzalutamide

Patient-individual treatment with selection of abiraterone, enzalutamide, cabazitaxel and docetaxel; taking into account previous therapies as well as the marketing authorisation of the respective medicinal product.

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

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

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

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

1: To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.

2: If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.

3: As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.

4: The comparator therapy should be part of the appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge.

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

on 1. The antiandrogens bicalutamibe, cyproterone acetate and flutamide, the GnRH antagonists Abarelix and Degarelix, the GnRH-agonists buserelin, goserelin, histrelin, leuprorelin and triptorelin as well as other hormone therapeutics such as enzalutamide and abiraterone acetate and the cytostatic drugs estramustine, cabazitaxel, docetaxel and mitoxantrone are approved in the present therapeutic indication. Medicinal product with explicit marketing authorisation for hormone-sensitive prostate carcinoma are not included.

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

on 3. Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Radium-223-dichloride (resolution of 17 October 2019)
- Enzalutamide (resolution of 20 February 2014 and 18 June 2015)
- Abiraterone acetate (resolution of 29 March 2012 and 4 July 2013)
- Cabazitaxel (resolution of 29 March 2012:

on 4. The general state of medical knowledge, on which the finding of the G-BA is based, was illustrated by a systematic research for guidelines as well as reviews of clinical studies in the present therapeutic indication.

According to national and international guidelines, patients who have already received androgen receptor-targeted treatment as first-line therapy may be offered sequence therapy in the second-line setting, including abiraterone, cabazitaxel, enzalutamide or docetaxel (or radium-223-dichloride for bone metastasis). There are no recommendations for a preferred treatment sequence in the guidelines. Therefore, it cannot be conclusively assessed whether a second androgen receptor-targeted

treatment after progression under first-line treatment with the other active ingredient may be less effective than second-line chemotherapy with docetaxel. In subsequent lines of treatment, the medicinal products mentioned above and not previously used can be administered. There are no data to suggest an optimal treatment sequence.

Currently, there are no specific therapy recommendations depending on BRCA mutations.

Within the framework of the benefit assessment according to § 35a SGB V, the above-mentioned active ingredients abiraterone, cabazitaxel, enzalutamide and radium-223-dichloride were assessed. In this context, the partly different therapeutic indications have to be considered, which address different therapy situations as well as partly certain features, e.g. an asymptomatic or mildly symptomatic course of the disease. For cabazitaxel, an indication of minor additional benefit was identified in a resolution dated 29 March 2012, compared with best supportive care. In the respective benefit assessments, abiraterone was assessed with an indication of a considerable additional benefit compared with best supportive care or the wait-and-see approach in resolutions dated 29 March 2012 and 4 July 2013, respectively. Enzalutamide showed evidence of considerable additional benefit compared with best supportive care (resolution of 20.2.2014). An indication of a considerable additional benefit was also found for enzalutamide compared with monitoring wait-and-see approach (resolution of 18.6.2015). The additional benefit of radium-223-dichloride was assessed as not proven for 2 patient groups compared with patient-individual treatment selecting abiraterone, enzalutamide, cabazitaxel, and docetaxel or compared with best supportive care by resolution dated 17/10/2019.

In the national and international guidelines, the medicinal products abiraterone, cabazitaxel, enzalutamide or docetaxel are recommended for the presently formulated therapeutic indication. However, there are no recommendations for a preferred treatment sequence, which is why no uniform treatment standard can be named for the patient population in question at present. Furthermore, the different previous therapies of the patients, including previous chemotherapy (especially with docetaxel), must be taken into account. On this basis, a patient-individual therapy is determined, selecting abiraterone, enzalutamide, cabazitaxel and docetaxel; taking into account previous therapies as well as the marketing authorisation of the respective medicinal product as appropriate comparator therapy.

According to the present guidelines, radiotherapy is of importance in the present therapeutic situation for the specific treatment of symptomatic bone metastases and only as a component of the overall oncological concept. Against this background, radiotherapy is not an option within the appropriate comparator therapy.

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

2.1.3 Extent and probability of the additional benefit

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

Adult patients with metastatic castration-resistant prostate cancer (mCRPC); BRCA1/2-mutated (germline and/or somatic); progressive disease after previous treatment with abiraterone and/or enzalutamide

Hint for a considerable additional benefit.

Justification:

For the benefit assessment, the pharmaceutical company submits the results of the open randomised controlled trial PROfound comparing olaparib versus abiraterone or enzalutamide.

The study included adult men with metastatic castration-resistant prostate cancer (mCRPC) and a mutation in a gene involved in homologous recombination repair (HRR). In addition, the disease had to be progressive under previous therapy with a new hormonal substance. Pretreatment was initially limited to the metastatic stage. With the protocol amendment of 4/6/2018, patients with pretreatment castration-resistant prostate cancer - without further restriction to metastatic stage - were also included during the course of the study. Patients should have radiographic progression on existing ADT (androgen deprivation therapy; drug or surgical castration) at the time of study inclusion.

A total of 387 men were included in the study, who were assigned to cohort A (BRCA1, BRCA2, Ataxia Telangiectasia Mutated (ATM)) or cohort B (other genes involved in HRR) depending on the mutation. Within cohorts, patients were randomly assigned in a 2:1 ratio to either treatment with olaparib or the corresponding therapy of the physician's choice (abiraterone or enzalutamide). The therapy with olaparib as well as abiraterone or enzalutamide was carried out under continuation of the existing androgen deprivation therapy (ADT), if there was no bilateral orchiectomy. Treatment with abiraterone was additionally combined with prednisone or prednisolone as appropriate. For the benefit assessment, the pharmaceutical company submits evaluations for the sub-population of patients with BRCA1/2-mutation. This sub-population included a total of 160 patients, 102 patients in the intervention arm and 58 patients in the comparator arm.

Until the first data cut-off, treatment with the study medication should be continued until radiological progression has been confirmed by a blinded independent review committee according to RECIST criteria version 1.1 or PCWG3 criteria. After this time, the principal investigator's assessment took place. Other discontinuation criteria were unacceptable toxicity, occurrence of myelodysplastic syndrome MDS or acute myeloid leukaemia, patient choice, clear clinical progression, or initiation of unauthorised cancer therapy.

The choice of subsequent therapies was at the discretion of the physician. For patients in the comparator arm, it was possible to receive olaparib after disease progression. Until the second data cut-off, 69% of patients in the comparator arm had received olaparib. At the time of study conduct, olaparib was not an approved treatment option as a subsequent therapy.

The primary endpoint of the study is radiologically confirmed progression-free survival (PFS); patient-relevant secondary endpoints include overall survival and endpoints on morbidity, health-related quality of life and adverse events (AEs).

For the present benefit assessment, the results of the 2nd evaluation phase are used. Data cut-off dated 20/3/2020 used, which is the planned final analysis for the overall survival endpoint after approximately 146 deaths.

In the PROfound study, the appropriate comparator therapy was implemented only for the subpopulation of patients for whom abiraterone and enzalutamide are best suited on a patient-individual basis. For the patient population for which docetaxel or cabazitaxel is most appropriate in the context of patient-individual therapy, the pharmaceutical company has not submitted any data. However, as no sufficiently suitable criteria can be identified for dividing the patient group into patients for whom patient-individual abiraterone or enzalutamide is most suitable and patients for whom patient-individual docetaxel or cabazitaxel is most suitable, the present results are used to assess the additional benefit for the entire patient population in the present therapeutic indication.

Extent and probability of the additional benefit

Mortality

The overall survival is defined as the time from randomisation to death from any cause.

For the endpoint overall survival, there is a significant difference between the treatment groups in favour of olaparib.

The achieved prolongation of overall survival in the comparison of olaparib versus abiraterone or enzalutamide is assessed as a significant improvement.

Morbidity

Progression-free survival

Radiographic progression-free survival (PFS) represented the primary endpoint of the PROfound study and was operationalised as the time from randomisation to radiologically detected progression or death regardless of the underlying cause of death. The assessment was independent of whether the patient discontinued study medication or received other antitumor therapy previous to progression. The occurrence of disease progression was assessed by imaging techniques and based on the RECIST criteria (version 1.1). The evaluation was conducted by a central, blinded, independent committee (BICR).

The result shows a statistically significant prolongation of PFS by treatment with olaparib compared to abiraterone or enzalutamide.

The endpoint component Mortality is already surveyed via the endpoint Overall survival as an independent endpoint. The morbidity component “Disease progression” was assessed solely by means of imaging procedures (radiologically determined disease progression according to the RECIST criteria). Thus, morbidity is not primarily assessed on the basis of disease symptoms, but solely on the basis of asymptomatic findings that are not directly relevant to the patient.

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the additional benefit remains unaffected.

Pain (BPI-SF)

In the PROfound study, a assessment of pain was conducted using the Brief Pain Inventory-Short Form (BPI-SF) questionnaire.

Worst pain (BPI-SF item 3)

In the dossier, the pharmaceutical company presented responder analysis on "time to first pain progression", operationalised as the time from randomisation to simple pain progression according to question 3 of the BPI-SF (strongest pain) by ≥ 2 points.

The data submitted by the pharmaceutical company in the written statement procedure show that the proportion of patients who were censored at day 1 because either no value was available at baseline and/or no follow-up value was 25.5% in the intervention arm and 22.4% in the comparator arm.

The results show a significant improvement in the endpoint "strongest pain" with treatment with olaparib compared to abiraterone or enzalutamide.

Pain intensity (BPI-SF items 3-6)

In the dossier, the pharmaceutical company presented responder analysis on "time to first worsening of pain," defined as the time from randomisation to worsening of pain according to questions 3-6 of the BPI-SF (strongest, least severe, average, and momentary pain) by ≥ 2 points.

The results show a significant improvement in the endpoint "Pain intensity" with treatment with olaparib compared to abiraterone or enzalutamide. The endpoint "Pain intensity" is presented as a supplement.

Impairment due to pain (BPI-SF item 9a-g)

In the dossier, the pharmaceutical company presented MMRM (mixed model for repeated measures analysis) analysis of the "mean change from baseline in impairment due to pain."

The standardised mean difference in the form of Hedges'g is used to assess the relevance of the result. The 95% confidence interval of the mean difference is completely outside the irrelevance range [−0.2; 0.2]. Thus, for the endpoint "Impairment due to pain" a relevant effect to the advantage of olaparib can be derived.

With its statement, the pharmaceutical company clarified that in the evaluations presented in the dossier for the endpoint "Impairment due to pain", only those observations were taken into account if, at the respective visit, ≥ 25% of the patients in both treatment arms had values for the change at baseline. In its statements, the pharmaceutical company submitted evaluations in which all visits are taken into account. Data subsequently submitted by the pharmaceutical company indicate that the proportion of patients censored at day 1 due to either no value at baseline and/or no follow-up value was 25.5% in the intervention arm and 22.4% in the comparator arm. For the endpoint "Impairment due to pain", a statistically significant difference between the treatment groups in favour of olaparib was also shown on the basis of the subsequently submitted analysis.

Symptomatic skeletal-related events

The endpoint "Symptomatic skeletal-related events" is a composite endpoint composed of the four individual components "new symptomatic pathological bone fractures", "radiotherapy to prevent or alleviate skeletal symptoms", "occurrence of spinal cord compression" and "orthopaedic surgery for bone metastases".

In the dossier, the pharmaceutical company presented responder analysis, operationalised as time from randomisation to the start of the first single component.

For the single component "occurrence of spinal cord compression", there was an advantage for olaparib over abiraterone or enzalutamide. There was no statistically significant difference between the treatment groups with regard to the individual components "new symptomatic pathological bone fractures", "radiotherapy to prevent or alleviate skeletal symptoms" and "orthopaedic surgery for bone metastases".

Health status (EQ-5D VAS)

In the PROfound study, health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

In the dossier, the pharmaceutical company presented steady evaluations and responder analysis, operationalised as time to permanent deterioration. These are not used because the proportion of patients not included in the analysis is > 30% and therefore not usable for the present benefit assessment.

Conclusion on morbidity

Overall, there are advantages in favour of olaparib for the patient-reported endpoints "Strongest pain" and "Impairment due to pain" as well as for the endpoint "Occurrence of spinal cord compression". No usable analysis are available for the endpoint health status measured with the EQ-5D VAS scale. Overall, a relevant advantage in therapeutic benefit can be derived for olaparib in the morbidity category.

Quality of life

FACT-P

Health-related quality of life was assessed in the PROfound study using the FACT-P questionnaire.

In the dossier, the pharmaceutical company presented continuous evaluations and responder analysis, operationalised as time to deterioration in quality of life. These are not used because the proportion of patients not included in the analysis is > 30% and therefore not usable for the present benefit assessment.

Side effects

Adverse events

The results for the endpoint total adverse events are only presented supplementary.

In the PROfound study, 97.1% of patients in the intervention arm and 89.7% of patients in the comparator arm experienced an adverse event.

Serious AEs

There was no statistically significant difference in serious adverse events between the two treatment arms.

Severe AE (CTCAE grade ≥ 3)

There was no statistically significant difference between treatment arms in the time to severe adverse events with CTCAE grade ≥ 3.

Discontinuation due to AE

There was no statistically significant difference in median time to treatment discontinuation due to AE between treatment arms.

PRO-CTCAE

For the endpoint PRO-CTCAE, the pharmaceutical company did not submit any data in the dossier. In its written statement, the pharmaceutical company explains that the results for the endpoint PRO-CTCAE are not usable due to a low proportion of patients included in the evaluation and refers to the study report for details. The G-BA is of the opinion that the data on the endpoint PRO-CTCAE would in principle be usable with regard to the proportion of patients included in the evaluation. However, only descriptive data are available, and, moreover, they refer to the entire study population. However, information on the relevant sub-population of patients with BRCA1/2-mutation is not presented.

Therefore, no usable results for the endpoint PRO-CTCAE are available for the benefit assessment.

Specific AE

The selection of specific AEs was done according to the methodology of the IQWiG using events based on frequency and differences between treatment arms and taking into account patient relevance.

Looking at the specific AEs in detail, there is a statistically significant difference to the disadvantage of olaparib versus abiraterone or enzalutamide for the specific AEs “anaemia” (PT, severe AEs) and “nausea” (PT, severe AEs). No data are available on the specific AEs “MDS” (PT, AEs) and “AML” (PT, AEs). No usable evaluations are available for the specific AE “pneumonitis” (PT, AEs).

In the overall consideration of the endpoints on Side effects, statistically significant disadvantages of olaparib are shown in detail for the specific AEs “anaemia” and “nausea”. Overall, neither an advantage nor a disadvantage is found for treatment with olaparib in the area of adverse events.

<u>Overall assessment</u>

For the benefit assessment of olaparib for the treatment of metastatic castration-resistant prostate cancer with BRCA1/2-mutation, the pharmaceutical company presented results of the PROfound study on the endpoint categories Mortality, Morbidity, Health-related quality of life and Side effects.

In the PROfound study, the appropriate comparator therapy was implemented only for the subpopulation of patients for whom abiraterone and enzalutamide are best suited on a patient-individual basis. Due to insufficiently appropriate criteria for dividing the patient group into patients for whom abiraterone or enzalutamide or docetaxel or cabazitaxel is best suited on a patient-individual basis, the present results are used to assess the additional benefit for the entire patient population in the present therapeutic indication.

For the endpoint Overall survival, olaparib showed a statistically significant advantage over abiraterone or enzalutamide, which can be considered a significant improvement.

In the area of morbidity, the endpoints “strongest pain” and “impairment due to pain” as well as the endpoint component “occurrence of spinal cord compression” showed an advantage for treatment with olaparib. Overall, an advantage for olaparib can be derived.

No usable evaluations are available for the quality of life category.

In the endpoints on Side effects, despite the disadvantages in the specific AEs “anaemia” and “nausea”, overall neither an advantage nor a disadvantage for treatment with olaparib be determined.

Overall, olaparib showed a significant improvement in overall survival and other relevant benefits in patient-reported morbidity endpoints. Neither advantages nor disadvantages can be derived from the side effects. Therefore, overall, despite the unusable data on quality of life, a considerable additional benefit can be derived for olaparib for the treatment of metastatic, castration-resistant prostate carcinoma with BRCA1/2-mutation compared with the appropriate comparator therapy.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the open-label, randomised, controlled phase III PROfound study.

At the endpoint level, the risk of bias in overall survival is considered high due to the high cross-over rate from the comparison arm to the intervention arm. In this respect, however, the uncertainty is not considered to be of such relevance as to justify a downgrading of the reliability of the overall assessment.

All other endpoints have a high risk of bias due to the open study design.

A relevant uncertainty exists in that the available data basis only includes the comparison with a part of the patient-individual therapy options in the present therapeutic indication according to the appropriate comparator therapy or does not allow statements on a comparison with taxanes (docetaxel or cabazitaxel) taking into account the previous therapies.

Overall, these limitations lead to the reliability of the additional benefit being classified as “hint”.

2.1.4 Summary of the assessment

“Lynparza is indicated as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior treatment that included a new hormonal agent.”

The appropriate comparator therapy was determined to be a patient-individual therapy with a choice of abiraterone, enzalutamide, cabazitaxel and docetaxel, taking into account the previous therapies as well as the marketing authorisation of the respective medicinal product.

The pharmaceutical company submits the results of the open RCT PROfound for the benefit assessment. In the study, the appropriate comparator therapy was implemented only for the subpopulation of patients for whom abiraterone or enzalutamide is best suited on a patient-individual basis. Due to insufficiently suitable criteria for a division of the patient population, the present results are used for the assessment of the additional benefit for the entire patient population in the present therapeutic indication.

There is a statistically significant prolongation of overall survival.

In terms of morbidity, relevant benefits for olaparib were observed for patient-reported endpoints and symptomatology.

No usable analysis are available for the endpoint category Quality of life.

In the endpoint category Side effects, neither advantages nor disadvantages were shown for olaparib.

The reliability of the data is assessed as a hint, among other things because the available data basis only includes the comparison with a part of the patient-individual therapy options in the present therapeutic indication according to the appropriate comparator therapy and does not allow statements on a comparison with taxanes (docetaxel or cabazitaxel) taking into account the previous therapies.

As a result, the G-BA found hint of considerable additional benefit for olaparib compared with the appropriate comparator therapy.

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 derivation of the patient numbers carried out by the pharmaceutical company in the dossier is mathematically comprehensible, but there are under- or overestimations in individual steps:

By using the 10-year prevalence, patients who have had prostate cancer for more than 10 years were not included.

The proportion of patients with metastatic castration-resistant prostate cancer (mCRPC) is more likely to be overestimated, taking into account the derivation of the target population from previous methods. For the lower limit of the proportion value, an overestimation can be assumed, since only the most recent patients undergoing treatment with medication were recorded, in which the proportion of patients with mCRPC may be higher than if all patients with prostate carcinoma were taken into account. The upper limit of the proportion value can also be assumed to be an overestimate, as only patients who received active or palliative treatment were recorded, and it is assumed that patients with mCRPC visit a practice more frequently compared with patients in an earlier stage of the disease.

The proportion of patients with mCRPC who received pretreatment with a new hormonal therapy is assumed to be underestimated, as only the directly preceding therapy of drug-treated patients was recorded.

In addition, the proportion of patients with a BRCA1/2-mutation is subject to uncertainty.

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 March 2021):

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

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

Medicinal castration with a GnRH agonist or antagonist should be continued during the treatment of patients who have not been surgically castrated.

Prior to initiation of therapy with Lynparza, patients with BRCA1/2-mutated metastatic castration-resistant prostate cancer must have evidence of a deleterious or suspected deleterious BRCA1/2-mutation. BRCA1/2-mutation status should be detected by an experienced laboratory using a validated test method. Patients who test positive for mutation of the BRCA1/2 genes should be offered genetic counselling according to national regulations.

2.4 Treatment costs

The treatment costs are based on the information of the product information as well as the information in the Lauer-Taxe (status: 15 May 2021).

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

Treatment duration:

Name of therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/ treatment (days)	Days of treatment/ Patient/ Year
Medicinal product to be assessed				
Olaparib	continuously, twice a day	365	1	365
LHRH analogue				
Degarelix	Continuously, once a month	12	1	12
Buserelin	continuous, every 3 months	4	1	4
Goserelin	continuous, every 3 months	4	1	4
Leuprorelin	continuous, every 3 months	4	1	4

Name of therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/ treatment (days)	Days of treatment/ Patient/ Year
Triptorelin	continuous, every 6 months	2	1	2
Appropriate comparator therapy				
Abiraterone acetate + prednisone or prednisolone + LHRH analogue				
Abiraterone acetate	continuously, once daily	365	1	365
Prednisolone or prednisone	continuously, once daily	365	1	365
LHRH analogue				
Degarelix	Continuously, once a month	12	1	12
Buserelin	continuous, every 3 months	4	1	4
Goserelin	continuous, every 3 months	4	1	4
Leuprorelin	continuous, every 3 months	4	1	4
Triptorelin	continuous, every 6 months	2	1	2
Enzalutamide + LHRH analogue				
Enzalutamide	continuously, once daily	365	1	365
LHRH analogue				
Degarelix	Continuously, once a month	12	1	12
Buserelin	continuous, every 3 months	4	1	4
Goserelin	continuous, every 3 months	4	1	4
Leuprorelin	continuous, every 3 months	4	1	4
Triptorelin	continuous, every 6 months	2	1	2
Cabazitaxel + prednisone or prednisolone				

Name of therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/ treatment (days)	Days of treatment/ Patient/ Year
Cabazitaxel	once every 21 days	17.4	1	17.4
Prednisolone or prednisone	continuously, once daily	365	1	365
Docetaxel + prednisone or prednisolone				
Docetaxel	once every 21 days	17.4	1	17.4
Prednisolone or prednisone	continuously, twice a day	365	1	365

Consumption:

For doses depending on body weight (BW) or body surface area (BSA), the average body measurements for adult men was used (average height: 1.79 m, average body weight: 85 kg). This results in a body surface area of 2.04 m² (calculated according to Du Bois 1916)[2].

Name of therapy	Dosage/ Application	Dosage/patient/days of treatment	Usage by strength/day of treatment	Days of treatment / Patient/ Year	Average annual consumption by potency
Medicinal product to be assessed					
Olaparib	300 mg	600 mg	4 x 150 mg	365	1,460 x 150 mg
LHRH analogue					
Degarelix	80 mg	80 mg	1 x 80 mg	12	12 x 80 mg
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4	4 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4	4 x 11.25 mg

[2] Statistisches Bundesamt (Federal Statistic Office) Microcensus questions on health - body measurements of the population 2018 https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Gesundheitszustand-Relevantes-Verhalten/Publikationen/Downloads-Gesundheitszustand/koerpermasse-5239003179004.pdf?__blob=publicationFile

Name of therapy	Dosage/ Application	Dosage/patient/days of treatment	Usage by strength/day of treatment	Days of treatment / Patient/ Year	Average annual consumption by potency
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2	2 x 22.5 mg
Appropriate comparator therapy					
Abiraterone acetate + prednisone or prednisolone + LHRH analogue					
Abiraterone acetate	1,000 mg	1,000 mg	2 x 500 mg	365	730 x 500 mg
Prednisolone or prednisone	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
LHRH analogue					
Degarelix	80 mg	80 mg	1 x 80 mg	12	12 x 80 mg
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4	4 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2	2 x 22.5 mg
Enzalutamide + LHRH analogue					
Enzalutamide	160 mg	160 mg	4 x 40 mg	365	1,460 x 40 mg
LHRH analogue					
Degarelix	80 mg	80 mg	1 x 80 mg	12	12 x 80 mg
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4	4 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2	2 x 22.5 mg
Cabazitaxel + prednisone or prednisolone					
Cabazitaxel	25 mg/m² bw = 51 mg	51 mg	1 x 60 mg	17.4	17.4 x 60 mg
Prednisolone or prednisone	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg

Name of therapy	Dosage/ Application	Dosage/patient/days of treatment	Usage by strength/day of treatment	Days of treatment / Patient/ Year	Average annual consumption by potency
Docetaxel + prednisone or prednisolone					
Docetaxel	75 mg/m² bw = 153 mg	153 mg	1 x 160 mg	17.4	17.4 x 160 mg
Prednisolone or prednisone	5 mg	5 mg	2 x 5 mg	365	730 x 5 mg

Costs

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

Cost of medicinal product:

Name of therapy	Package size	Costs Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate § 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Olaparib	112 FCT	€ 5,616,98	€ 1,77	€ 317,51	€ 5,297,70
Degarelix 80 mg	3 PSI	€ 571,38	€ 1,77	€ 31,02	€ 538,59
Buserelin 9,45 mg	2 PS	€ 1,027,87	€ 1,77	€ 56,30	€ 969,80
Goserelin 10.8 mg	2 IMP	€ 1,013,29	€ 1,77	€ 55,49	€ 956,03
Leuprorelin 11.25 mg	2 IMP	€ 730,51	€ 1,77	€ 86,93	€ 641,81

Triptorelin 22.5 mg	1 DSS	€ 944,17	€ 1,77	€ 51,66	€ 890,74
Appropriate comparator therapy					
Abiraterone acetate	56 FCT	€ 3,518,47	€ 1,77	€ 0,00	€ 3,516,70
Prednisolone 10 mg[3]	100 TAB	€ 17,54	€ 1,77	€ 0,51	€ 15,26
Prednisone 10 mg[3]	100 TAB	€ 20,96	€ 1,77	€ 0,78	€ 18,41
Degarelix 80 mg	3 PSI	€ 571,38	€ 1,77	€ 31,02	€ 538,59
Buserelin	2 PS	€ 1,027,87	€ 1,77	€ 56,30	€ 969,80
Goserelin	2 IMP	€ 1,013,29	€ 1,77	€ 55,49	€ 956,03
Leuprorelin	2 IMP	€ 730,51	€ 1,77	€ 86,93	€ 641,81
Triptorelin	1 DSS	€ 944,17	€ 1,77	€ 51,66	€ 890,74
Enzalutamide	112 FCT	€ 3,455,99	€ 1,77	€ 0,00	€ 3,454,22
Cabazitaxel	1 IFK	€ 3,573,61	€ 1,77	€ 172,13	€ 3,399,71
Docetaxel	1 IFK	€ 1,397,36	€ 1,77	€ 175,44	€ 1,220,15
Prednisolone 5 mg[3]	100 TAB	€ 15,16	€ 1,77	€ 0,33	€ 13,06
Prednisone 5 mg[3]	100 TAB	€ 16,47	€ 1,77	€ 0,43	€ 14,27
Abbreviations: PS = prefilled syringes; FTA = film-coated tablets, IFK = concentrate for infusion; ILO = solution for injection; PSI = powder and solvent for solution for injection; IMP = implant; TAB = tablets; DSS = dry substance with solvent					

Stand Lauer-Taxe: 15 May 2021

Costs for additionally required SHI services:

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

3fixed reimbursement rate

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

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

3. Bureaucratic cost calculation

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

4. Process sequence

At its session on 10 December 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 17 November 2020.

On 30 November 2020, the pharmaceutical company submitted a dossier for the benefit assessment of olaparib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2, sentence 2 VerfO.

By letter dated 2 December 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient olaparib.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 March 2021, and the written statement procedure was initiated with publication on the G-BA website on 15 March 2021. The deadline for submitting written statements was 6 April 2021.

The oral hearing was held on 27 April 2021.

By letter dated 27 April 2021, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 12 May 2021.

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

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 25 May 2021, and the draft resolution was approved.

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

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	10 December 2019	Implementation of the appropriate comparator therapy
Working group Section 35a	17 November 2020	Implementation of the appropriate comparator therapy
Working group Section 35a	13 April 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal product	27 April 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	4 May 2021 18 May 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal product	25 May 2021	Final discussion of the draft resolution
Plenum	3 June 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 3 June 2021

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

Prof. Hecken