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: prostate cancer, metastatic, castration-resistant chemotherapy not clinically indicated, combination with abiraterone and/or prednisone)

of 6 July 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 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 on 1 June 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 16 December 2022, AstraZeneca GmbH received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2a, letter a to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 13 January 2023, 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 of treatment of adult patients with mCRPC, in whom chemotherapy is not clinically

indicated, 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 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 IQWiG 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 in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated.

Therapeutic indication of the resolution (resolution of 06.07.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC

Appropriate comparator therapy for olaparib in combination with abiraterone and prednisone or prednisolone:

- abiraterone acetate in combination with prednisone or prednisolone (only for patients whose disease is progressive during or after docetaxel-containing chemotherapy; only for patients with asymptomatic or mildly symptomatic disease after failure of androgen deprivation therapy, in whom chemotherapy is not yet clinically indicated)

  or

- enzalutamide (only for patients whose disease progresses during or after chemotherapy with docetaxel; only for patients with asymptomatic or mildly

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

symptomatic disease after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated)

or

– olaparib as monotherapy (only for patients with BRCA1/2 mutations (germline and/or somatic) whose disease is progressive after previous treatment that included a new hormonal agent)

or

– best supportive care (only for patients with reduced general condition (ECOG performance status ≥ 2))

b) Adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated and who have received prior therapy for mCRPC

Appropriate comparator therapy for olaparib in combination with abiraterone and prednisone or prednisolone:

Patient-individual therapy with selection of:

- abiraterone acetate in combination with prednisone or prednisolone (only for patients whose disease is progressive during or after docetaxel-containing chemotherapy),
- enzalutamide (only for patients whose disease progresses during or after chemotherapy with docetaxel) and
- olaparib as monotherapy (only for patients whose disease is progressive after previous treatment that included a new hormonal agent),

taking into account the previous therapy/ therapies and the BRCA1/2 mutational status.

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 terms of the authorisation status, the active ingredients bicalutamide, cyproterone acetate, flutamide, degarelix, buserelin, goserelin, leuprorelin, triptorelin, enzalutamide, abiraterone acetate, estramustine, cabazitaxel, docetaxel, mitoxantrone, lutetium (^{177}Lu) vipivotide tetraxetan and radium-223-dichloride are available for the treatment of castration-resistant prostate cancer. Medicinal products with explicit marketing authorisation for hormone-sensitive prostate cancer are not considered.

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

on 3. For metastatic castration-resistant prostate cancer, resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V on the active ingredients olaparib (monotherapy), radium-223-dichloride, enzalutamide, abiraterone acetate and cabazitaxel are available.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

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 indication according to Section 35a, paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy").

Against the background that the patients are treated with olaparib in combination with abiraterone acetate and prednisone or prednisolone according to the present therapeutic indication, it was assumed when determining the appropriate comparator therapy that the individual therapeutic decision in the target population was made against a sole continuation of conventional androgen deprivation ("wait-and-see approach"). The wait-and-see approach while maintaining the existing conventional androgen deprivation (ADT) is therefore not considered an appropriate comparator therapy in the present case. However, it is assumed that an existing conventional ADT will be continued. In the context of the present therapeutic indication, conventional ADT refers to surgical or medicinal castration by therapy with GnRH agonists or GnRH antagonists.

Furthermore, the present therapeutic indication generally addresses the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC), regardless of whether the patients have received prior treatment for mCRPC. Therefore, the G-BA considers it appropriate to divide the therapeutic indication into patients without prior treatment of mCRPC (patient group a)) and those after prior treatment of mCRPC (patient group b)).

The present therapeutic indication is also aimed at patients in whom chemotherapy is not clinically indicated. Suitability for chemotherapy is not a clearly defined variable, or the indication for chemotherapy cannot be clearly defined. In accordance with the approved therapeutic indication, the individual therapeutic decision at the time of therapy with olaparib in combination with abiraterone acetate and prednisone or prednisolone in the target population has been made against chemotherapy. A chemotherapy is therefore not considered to be the appropriate comparator therapy in the present case.

a) Initial therapy of mCRPC

The active ingredients abiraterone acetate (in combination with prednisone or prednisolone) and enzalutamide are explicitly approved for use in patients without prior treatment with docetaxel in an asymptomatic or mildly symptomatic course. However, guidelines recommend abiraterone acetate (in combination with prednisone or prednisolone) and enzalutamide, regardless of whether the patient is asymptomatic or mildly symptomatic. A regular preference for one of these active ingredients over the other active ingredients cannot be determined overall. However, the present therapeutic indication for olaparib in combination with abiraterone and prednisone or prednisolone also includes patients with symptomatic disease. Therefore, there is a discrepancy between medicinal products approved in the indication and those used in health care/ recommended in guidelines.

In the respective benefit assessments, both for abiraterone acetate (in combination with prednisone or prednisolone) by resolution of 04.07.2013 and for enzalutamide by resolution of 18.06.2015, an indication of a considerable additional benefit was identified compared to the wait-and-see approach while maintaining the existing conventional androgen deprivation.

In determining the appropriate comparator therapy, it is also taken into account that patients may have already received prior therapy with docetaxel or a novel hormonal agent (NHA) in earlier stages of the disease. In this regard, abiraterone acetate in combination with prednisone or prednisolone as well as enzalutamide are also approved for patients whose disease is progressive during or after docetaxel-containing chemotherapy. For this therapeutic indication, an indication of a considerable additional benefit compared to best supportive care was identified for abiraterone acetate by resolution of 29.03.2012 and for enzalutamide by resolution of 20.02.2014 for patients who are progressive during or after docetaxel-containing chemotherapy.

For patients who have already received prior therapy with NHA, olaparib as monotherapy is another therapeutic alternative recommended by the guidelines. The marketing authorisation is for patients with BRCA1/2 mutations (germline and/or somatic). In the benefit assessment, a hint for a considerable additional benefit was identified for olaparib compared to patient-individual therapy (resolution of 03.06.2021).

For patients with symptomatic mCRPC and a reduced general condition (ECOG performance status ≥ 2) who have limited suitability for treatment, symptom-based therapy should be offered according to the current S3 guideline[2] . Therefore, best supportive care is determined as the appropriate comparator therapy for these

[2] Oncology guideline programme, S3 guideline for prevention, diagnosis, therapy and follow-up of prostate cancer (version 6.2, October 2021)

patients. Best supportive care is defined as the therapy that provides the best possible, patient-individual, optimised supportive treatment to alleviate symptoms and improve quality of life.

Chemotherapy with docetaxel (in combination with prednisone or prednisolone) is not considered due to the present therapeutic indication.

In the overall assessment, the G-BA therefore determines abiraterone acetate in combination with prednisone or prednisolone, enzalutamide, olaparib as monotherapy or best supportive care as equally appropriate comparator therapies for patients with mCRPC who have not yet received prior therapy for mCRPC and in whom chemotherapy is not clinically indicated.

The appropriate comparator therapy determined here includes several therapeutic alternatives. In this context, individual therapeutic alternatives only represent a comparator therapy for the part of the patient population that has the patient and disease characteristics specified in brackets. The therapeutic alternatives are only to be considered equally appropriate in the therapeutic indication, where the patient populations have the same characteristics.

These guidelines list both approved and unapproved medicinal therapies for the initial treatment of mCRPC in symptomatic patients. Medicinal products that do not have a marketing authorisation for the present indication and whose prescribability in off-label use has also not been recognised by the G-BA in the Pharmaceuticals Directive are generally not considered as appropriate comparator therapy in the narrower sense of Section 2, paragraph 1, sentence 3, Section 12 SGB V according to the statements by the Federal Social Court (FSC) on the judgement of 22.02.2023 (file ref.: B 3 KR 14/21 R).

b) after previous therapy of mCRPC

For adult patients with mCRPC who have received prior therapy for mCRPC, further targeted treatment is recommended according to the present guidelines, especially taking into account the prior therapy/ therapies. In determining the appropriate comparator therapy, it is assumed in this context that patients may have already received further prior therapy with docetaxel or NHA in earlier stages of the disease in addition to the previous therapy for mCRPC. Although there are no recommendations for a standard treatment sequence in the guidelines, the main plea is for a change in treatment strategy, taking into account an alternative mode of action. The treatment decision is thus made in particular on the basis of the previous patient-individual therapy/ therapies to be taken into account.

Patients who have already received androgen receptor-targeted treatment with abiraterone acetate in combination with prednisone or prednisolone or enzalutamide as therapy can be offered sequence therapy in the further line, taking into account the previously non-administered active ingredient. Therefore, the previous androgen receptor-targeted treatment received by the patients must be taken into account. However, the guidelines cannot conclusively assess whether a second androgen receptor-targeted treatment after progression under first-line treatment with the other active ingredient may be less effective than chemotherapy with docetaxel in the second line. Both active ingredients are explicitly approved for use in patients without prior treatment with docetaxel in an asymptomatic or mildly symptomatic course.

For patients who have already received prior therapy with NHA, olaparib as monotherapy is another therapeutic alternative recommended by the guidelines. The

marketing authorisation is for patients with BRCA1/2 mutations (germline and/or somatic). In the benefit assessment, a hint for a considerable additional benefit was identified for olaparib (as monotherapy) compared with patient-individual therapy (resolution of 03.06.2021).

Furthermore, abiraterone acetate in combination with prednisone or prednisolone is approved for patients whose disease is progressive during or after docetaxel-containing chemotherapy and is recommended in the guidelines. By resolution of 29 March 2012, an indication of a considerable additional benefit compared to best supportive care was identified for this therapeutic indication for patients who are progressive during or after chemotherapy containing docetaxel and for whom renewed treatment with docetaxel is no longer an option.

Enzalutamide is also approved for the treatment of patients whose disease progresses during or after chemotherapy with docetaxel. In the associated benefit assessment, an indication of a considerable additional benefit compared to best supportive care was identified by resolution of 20.02.2014.

Guidelines recommend abiraterone acetate (in combination with prednisone or prednisolone) and enzalutamide, regardless of whether the patient is asymptomatic or mildly symptomatic. However, the approved therapeutic indication for olaparib in combination with abiraterone acetate and prednisone or prednisolone also includes patients with symptomatic disease. There is a discrepancy between medicinal products approved in the indication and those used in healthcare/ recommended in guidelines.

For patients who are pretreated with a docetaxel-based therapy regimen, cabazitaxel in combination with prednisone or prednisolone is another approved therapeutic alternative recommended by guidelines for this treatment setting. In the benefit assessment, an indication of a minor additional benefit was identified for cabazitaxel in combination with prednisone or prednisolone for patients who are progressive during or after a chemotherapy containing docetaxel and in whom a renewed treatment with docetaxel is no longer an option (resolution of 29.03.2012).

Furthermore, docetaxel in combination with prednisone or prednisolone is approved for the treatment of patients with metastatic castration-resistant prostate cancer and is also recommended by the guidelines.

However, chemotherapy with docetaxel or with cabazitaxel (in each case in combination with prednisone or prednisolone) is not determined to be an appropriate comparator therapy due to the present therapeutic indication.

Lutetium (^{177}Lu) vipivotide tetraxetan is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved (marketing authorisation on 09.12.2022). Based on the generally accepted state of medical knowledge, lutetium (^{177}Lu) vipivotide tetraxetan is not determined to be an appropriate comparator therapy for the present resolution.

In the overall assessment, for patients with mCRPC who have already received prior therapy for mCRPC, the G-BA therefore determines a patient-individual therapy, selecting abiraterone acetate in combination with prednisone or prednisolone, enzalutamide and olaparib as monotherapy as an appropriate comparator therapy, taking into account the previous therapy/ therapies and BRCA1/2 mutational status.

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

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.

Change of the appropriate comparator therapy

Originally, the following appropriate comparator therapy was determined for the present therapeutic indication:

a) Adults with untreated metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated

Therapy according to doctor's instructions

The G-BA considered abiraterone acetate in combination with prednisone or prednisolone and enzalutamide to be suitable comparators without limitation in terms of symptomatology.

b) Adults with pretreated metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated

Patient-individual therapy taking into account prior therapy and the BRCA1/2 mutational status

In the context of this patient-individual therapy, abiraterone acetate in combination with prednisone or prednisolone, enzalutamide and olaparib (monotherapy) were considered suitable comparators.

However, the marketing authorisation of both abiraterone acetate in combination with prednisone or prednisolone and enzalutamide before chemotherapy restricts to asymptomatic to mildly symptomatic patients. After chemotherapy with docetaxel, abiraterone acetate in combination with prednisone or prednisolone and enzalutamide are approved without limitation in terms of symptomatology.

In this regard, the change in the appropriate comparator therapy is necessary due to the judgement passed by the Federal Social Court on 22.02.2023, file ref.: D 3 KR 14/21 R, as it considers the designation of medicinal products in off-label use as an appropriate comparator therapy to be fundamentally inadmissible if this does not comply with the requirements of appropriateness in the narrower sense within the meaning of Section 2, paragraph 1, sentence 3, Section 12 SGB V.

Olaparib is approved as monotherapy after pretreatment with a new hormonal substance in the present therapeutic indication and is determined as an appropriate comparator therapy based on the generally accepted state of medical knowledge in patients with mCRPC and BRCA mutation without pretreatment (patient group a)).

As a result of the restriction on authorisation to be considered for abiraterone acetate in combination with prednisone or prednisolone and for enzalutamide to asymptomatic to mildly symptomatic patients, further treatment options were required in the appropriate comparator therapy for symptomatic patients for whom abiraterone in combination with prednisone or prednisolone is not a therapeutic option, in order to cover the entire therapeutic indication. According to the recommendations of the German S3 guideline, symptom-based therapy (best supportive care) can also be considered for patients with

symptomatic, progressive disease and reduced general condition (ECOG performance status ≥ 2). For these reasons, best supportive care was added as a treatment option for patients with reduced general condition (ECOG performance status ≥ 2) in the appropriate comparator therapy.

This change in the appropriate comparator therapy has no impact on the present benefit assessment.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of olaparib in combination with abiraterone and prednisone or prednisolone is assessed as follows:

a) Adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC

a1) Adults with BRCA mutation

Hint for a considerable additional benefit.

a2) Adults without BRCA mutation (BRCA wild type)

An additional benefit is not proven.

Justification:

In order to demonstrate an additional benefit of olaparib in combination with abiraterone and prednisone or prednisolone for the treatment of men with castration-resistant metastatic prostate cancer (mCRPC), the pharmaceutical company presents the results of the 2nd data cut-off of the PROpel study from 14.03.2022 in the dossier. This study has been conducted since October 2018 in 126 study sites, in particular in Australia, Europe and North and South America.

The PROpel study is a randomised, controlled, double-blind phase III study comparing olaparib in combination with abiraterone and prednisone or prednisolone against abiraterone and prednisone or prednisolone.

The study enrolled a total of 796 adult patients with mCRPC who had not received any prior therapy at this stage of the disease and had good general condition, according to an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 or 1. Randomisation was 1:1 to treatment with olaparib in combination with abiraterone and prednisone or prednisolone (N = 399) or placebo with abiraterone and prednisone or prednisolone (N = 397), stratified by presence of metastases (bone only/ visceral/ other) and docetaxel pretreatment at mHSPC stage (yes/ no).

Treatment in both the intervention and control arms was according to the respective product information. According to the inclusion criteria, in addition to the study medication, patients should continue an existing ADT, either in the form of drug castration with gonadotropin-releasing hormone (GnRH) analogue or surgical castration by removal of both testicles.

The primary endpoint of the study is the radiologically confirmed progression-free survival (rPFS). Patient-relevant secondary endpoints were assessed in the categories of mortality, morbidity, health-related quality of life and side effects.

Within the framework of the written statement procedure, the pharmaceutical company submits the 3rd data cut-off of the PROpel study from 12.10.2022. Furthermore, additional data characterising the study population was also presented for the first time in the form of aggregated data on homologous recombination repair (HRR) and breast cancer susceptibility gene (BRCA) mutational status, with approximately one-third of patients having an HRR mutation and 10% of patients having a BRCA1/2 mutation. These subgroup analyses were not pre-specified, but were required by the European Medicines Agency (EMA) for the 3rd data cut-off and are therefore taken into account for the benefit assessment.

For all endpoints, the present assessment is based on the results of the 3rd data cut-off of 12 October 2022 submitted by the pharmaceutical company with its written statement.

However, it remains unclear what percentage of patients received concomitant androgen deprivation therapy (ADT). According to the inclusion criteria of the PROpel study, all patients had to have continuous therapy with a GnRH analogue or a bilateral orchiectomy within 28 days prior to randomisation and proceed with continuous therapy with a GnRH analogue. According to the study documents available from the dossier, concomitant treatment with GnRH analogues is documented exclusively for 53.9% of patients, and prior bilateral orchiectomy for 5.7% of patients. In the written statement procedure, the pharmaceutical company provided further information on the percentage of patients for whom ADT was continued, but this information varies between 74.7% and 91.1%, depending on how it is presented.

Extent and probability of the additional benefit

Analysis across endpoints

In the subgroup analyses on the characteristic "BRCA mutational status" (BRCA mutated vs BRCA wild type), significantly different effects were shown for the endpoints of overall survival, symptomatic skeletal-related events, health-related quality of life (assessed using FACT-P) and serious adverse events (SAEs) depending on the BRCA mutational status. Thus, this effect modification of the characteristic "BRCA mutational status" occurs consistently in several endpoints relevant for the present assessment.

Against this background, the G-BA considers it appropriate to conduct a separate assessment of the additional benefit for patients with BRCA mutation and without BRCA mutation (BRCA wild-type) on the basis of the effect modification that occurred with regard to the characteristic "BRCA mutational status".

Mortality

Overall survival was defined in the PROpel study as the time from randomisation to death from any cause, regardless of whether the patient had discontinued their assigned therapy in the study or was already receiving subsequent cancer therapy at the time of death. For this endpoint, there is no statistically significant difference between the treatment groups in the total population.

For patients with BRCA mutation, overall survival shows a statistically significant difference to the advantage of olaparib in combination with abiraterone and prednisone or prednisolone versus abiraterone and prednisone or prednisolone. In this regard, the extent of the prolongation achieved in overall survival is assessed as a very significant improvement.

For patients without BRCA mutation, there is no statistically significant difference between the treatment groups.

Morbidity

Progression-free survival

Radiological progression-free survival (rPFS) in the PROpel study was operationalised as the time from randomisation to the occurrence of one of the following events: radiologically detected progression as assessed by the principal investigators or the BICR, or death from any cause (in the absence of progression), regardless of whether the patient discontinued study medication or received other anti-tumour therapy prior to progression. Radiological progression was assessed via the RECIST 1.1 for soft tissue and the PCWG-3 for metastatic bone lesions. The data were collected by the principal investigator on the basis of a Blinded Independent Central Review (BICR).

Olaparib in combination with abiraterone and prednisone or prednisolone has a statistically significant prolonged rPFS compared to abiraterone in combination with prednisone or prednisolone in the total population.

The present rPFS endpoint is a combined endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component of "disease progression" is assessed according to RECIST as well as PCWG3 criteria and thus predominantly by means of imaging procedures.

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.

Worst pain (BPI-SF item 3) and pain intensity (BPI-SF items 3-6)

For the endpoints of worst pain, assessed by BPI-SF item 3, and pain intensity, assessed by BPI-SF items 3-6, there are no statistically significant differences between the treatment groups.

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

The endpoint of impairment due to pain was assessed using BPI-SF items 9a-g and operationalised as time to first deterioration with an increase of ≥ 1.5 points compared to the start of the study.

For patients with BRCA mutation, there is a statistically significant difference in the present endpoint, showing a relevant benefit of olaparib in combination with abiraterone and prednisone or prednisolone versus abiraterone and prednisone or prednisolone. For patients without BRCA mutation, there is no statistically significant difference between the treatment groups.

Health status (EQ-5D VAS)

For the endpoint of health status, assessed using the EQ-5D visual analogue scale (VAS), no usable data are available, as the percentage of patients who were censored on day 1 and thus not included in the analysis is > 30%.

Symptomatic skeletal-related events (SSRE)

The endpoint of symptomatic skeletal-related events was operationalised in the PROpel study as the time from randomisation to the first occurrence of one or a combination of the following skeletal-related complications:

- Radiotherapy to prevent or alleviate skeletal symptoms
- Occurrence of a new symptomatic, pathological bone fracture (both vertebral and non-vertebral)
- Occurrence of spinal cord compression. Radiological documentation had to be available
- Orthopaedic surgery due to bone metastases

For patients with BRCA mutation, the present endpoint shows a statistically significant difference, showing a clear advantage of olaparib in combination with abiraterone and prednisone or prednisolone over abiraterone and prednisone or prednisolone. For patients without BRCA mutation, there is no statistically significant difference between the treatment groups.

In the overall analysis of the results on morbidity, there are clear advantages for patients with BRCA mutation in the endpoints on symptomatology for olaparib in combination with abiraterone and prednisone or prednisolone compared to the appropriate comparator therapy.
In patients without BRCA mutation, there were no differences relevant to the benefit assessment. There is therefore neither an advantage nor a disadvantage of this patient population in terms of symptomatology.

Quality of life

FACT-P

Health-related quality of life was assessed in the PROpel study using FACT-P questionnaire, operationalised as the time to first deterioration with a decrease of ≥ 23.4 points compared to the start of the study. The FACT-P questionnaire consists of the cross-tumour disease questionnaire (FACT-G) and a prostate cancer-specific sub-scale (PCS). The FACT-G questionnaire in turn consists of four sub-scales: physical well-being, social/ family well-being, emotional well-being and functional well-being.

Only the total score of the FACT-P questionnaire is included in the assessment of the additional benefit as it comprehensively considers the data on the health-related quality of life of the patients. The individual sub-scales of the FACT-P are therefore only presented additionally.

For patients with BRCA mutation, there is a clear advantage of olaparib in combination with abiraterone and prednisone or prednisolone over abiraterone and prednisone or prednisolone.
For patients without a BRCA mutation, there is no statistically significant difference between the treatment groups, which means that there are neither advantages nor disadvantages for this patient group.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3), therapy discontinuations due to AEs

For the endpoint of serious AEs, there is no statistically significant difference between the treatment groups in the total population. For patients with BRCA mutation, there is no

statistically significant difference between the treatment groups, whereas there is a statistically significant disadvantage of olaparib in combination with abiraterone and prednisone or prednisolone compared to abiraterone in combination with prednisone or prednisolone in patients without BRCA mutation.

For the endpoints of severe AEs and therapy discontinuation due to AEs, there is a statistically significant disadvantage of olaparib in combination with abiraterone and prednisone or prednisolone compared to abiraterone in combination with prednisone or prednisolone in the total population.

Specific AEs

In detail, specific adverse events show statistically significant differences to the disadvantage of olaparib in combination with abiraterone acetate and prednisone or prednisolone with respect to diarrhoea (PT, AEs), nausea (PT, AEs), loss of appetite (PT, AEs), injury, poisoning and procedural complications (SOC, SAEs), pulmonary embolism (PT, severe AEs) and anaemia (PT, severe AEs) in the total population.

In summary, the side effects of olaparib in combination with abiraterone and prednisone or prednisolone show disadvantages due to the increase in severe AEs as well as therapy discontinuation due to AEs in the total population. In patients without a BRCA mutation, there is also a disadvantage due to the increase in SAEs.

In detail, negative effects of olaparib in combination with abiraterone and prednisone or prednisolone compared to abiraterone in combination with prednisone or prednisolone are seen for the specific AEs in the total population.

Overall assessment

a) Adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC

For the assessment of the additional benefit of olaparib in combination with abiraterone and prednisone or prednisolone in patients with metastatic castration-resistant prostate cancer without pretreatment, results on mortality, morbidity, health-related quality of life and side effects are available from the randomised, double-blind, multicentre, controlled PROpel study. The PROpel study compared olaparib in combination with abiraterone and prednisone or prednisolone versus abiraterone in combination with prednisone or prednisolone. The assessment is based on the 3rd data cut-off of the PROpel study from 12 October 2022, which had been requested by the European Medicines Agency (EMA).

In the sub-group analyses on the characteristic "BRCA mutational status" for the endpoints of overall survival, morbidity, health-related quality of life and serious adverse events (SAEs), there were clearly different effects depending on the BRCA mutational status. Thus, this effect modification of the characteristic "BRCA mutational status" occurs consistently in several endpoints relevant for the present assessment. Due to this effect modification, a separate assessment of the additional benefit is made for patients with BRCA mutation and patients without BRCA mutation (BRCA wild type):

a1) Adults with BRCA mutation

For the endpoint of overall survival, there is a statistically significant difference to the advantage of olaparib in combination with abiraterone and prednisone or prednisolone. The

extent of the prolongation achieved in overall survival in patients with BRCA mutation is assessed as a very significant improvement.

In the morbidity category, treatment with olaparib in combination with abiraterone and prednisone or prednisolone shows clear advantages for patients with BRCA mutation when considering the endpoints of impairment due to pain (assessed by BPI-SF item 9a-g) and symptomatic skeletal-related events (SSRE).

For health-related quality of life (assessed by FACT-P), there are clear advantages for olaparib in combination with abiraterone and prednisone or prednisolone in BRCA-mutated patients.

For the endpoint category of side effects, disadvantages can be observed for olaparib in combination with abiraterone and prednisone or prednisolone compared to abiraterone in combination with prednisone or prednisolone in the total population, especially for severe AEs, therapy discontinuation due to AEs and in detail for specific AEs.

The overall assessment shows advantages in mortality, morbidity and health-related quality of life. In contrast, there are disadvantages in the endpoint category of side effects. The balance identifies a considerable additional benefit of olaparib in combination with abiraterone and prednisone or prednisolone over abiraterone in combination with prednisone or prednisolone for patients with untreated metastatic castration-resistant prostate cancer with BRCA mutation.

a2) Adults without BRCA mutation (BRCA wild type)

In patients without a BRCA mutation, there is no statistically significant difference between the treatment groups in the endpoint category of overall survival.

In the endpoint category of morbidity, there are no statistically significant differences between the treatment groups in the endpoints of symptomatic skeletal-related events and pain (assessed by BPI-SF). The submitted data on health status (collected by EQ-5D VAS) are unsuitable.

For the endpoint category of side effects, there are disadvantages in the total population, particularly for severe AEs, therapy discontinuation due to AEs and in detail for specific AEs. Furthermore, patients without BRCA mutation show disadvantages in SAEs.

In the overall analysis of the results, there are neither advantages nor disadvantages in the endpoint categories of mortality, morbidity and health-related quality of life. In contrast, there are disadvantages in the endpoint category of side effects, especially SAEs. However, the extent of the negative effects is not considered to be so serious as to justify the derivation of a "lower benefit" in the overall analysis. For patients with untreated metastatic castration-resistant prostate cancer without BRCA mutation, an additional benefit of olaparib in combination with abiraterone and prednisone or prednisolone compared with abiraterone in combination with prednisone or prednisolone is therefore unproven.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the randomised, double-blind, multicentre controlled PROpel study.

It is unclear whether chemotherapy was not clinically indicated for all patients in the study population. Although it can be assumed that the percentage of asymptomatic/ mildly symptomatic patients and/or with docetaxel pretreatment is > 80%, uncertainty remains as to whether patients for whom chemotherapy would have been indicated were also enrolled in the study. Due to this relevant uncertainty, a reduced reliability of data is assumed for all endpoints.

In summary, the G-BA deduces a hint for the identified additional benefit with regard to the reliability of data (probability of additional benefit).

b) Adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated and who have received prior therapy for mCRPC

An additional benefit is not proven.

Justification:

For the treatment of adult males with pretreated metastatic castration-resistant prostate cancer in whom chemotherapy is not clinically indicated, the pharmaceutical company does not present any data for the assessment of additional benefit.

On the completeness of the dossier submitted

IQWiG stated in the dossier assessment that the data submitted by the pharmaceutical company for patient group b) are incomplete.

The pharmaceutical company did not submit any documents on study 8 in the dossier submitted as of 13 January 2023. It identified the study exclusively in the study register search and the bibliographic search and gave the population as the reason for exclusion. IQWiG was unable to assess the relevance of the study for patient group b) from this information.

Study 8, sponsored by the pharmaceutical company, investigated olaparib in combination with abiraterone and prednisone or prednisolone compared to abiraterone in combination with prednisone or prednisolone in patients with pretreated metastatic castration-resistant prostate cancer. This is a study in the approved therapeutic indication. The study was part of the authorisation documents and was used supportively by the EMA as part of the marketing authorisation. In accordance with the regulation pursuant to Chapter 5 Section 9, paragraph 4, sentence 1 of the Rules of Procedure of the G-BA, the pharmaceutical company must submit in the dossier the results report of the approval studies including the study protocols and the assessment report of the regulatory authority, as well as all studies that have been submitted to the regulatory authority. According to Section 9, paragraph 4, sentence 2 VerfO, studies sponsored/ financed by the pharmaceutical company must also be listed in the study list in the benefit assessment dossier.

In the written statement procedure, the pharmaceutical company submitted the complete study documents for study 8 in the written statement without any processing of the data in accordance with Chapter 5 Section 9, paragraph 2, sentence 2 VerfO. In this regard, it stated in the written and oral statements that study 8 was a single-comparator study that did not fulfil the requirements of the multi-comparator study demanded by the G-BA, and consequently did not represent the defined appropriate comparator therapy and was therefore unsuitable for the benefit assessment.

IQWiG assessed the relevance of study 8 for the benefit assessment on the basis of the study documents submitted in the written statement procedure, with the result that statements on a sub-population could have been derived from study 8. However, as the pharmaceutical company did not submit data in accordance with the module templates, IQWiG upholds the finding of incompleteness of the documentation.

The G-BA agrees with IQWiG's argument on the relevance of study 8 for patient group b) after a detailed discussion and, for its part, states that according to Chapter 5 Section 18, paragraph 1 of the Rules of Procedure of the G-BA, the preparation of the documents in the dossier

deviates to an extent from the requirements specified in Chapter 5, Section 9 VerfO des G-BA, which is contrary to a proper assessment of the additional benefit.

In accordance with the regulation in Chapter 5, Section 18 of the Rules of Procedure of the G-BA, the benefit assessment examines whether there is evidence of an additional benefit for the medicinal product compared to the appropriate comparator therapy. The validity and completeness of the information in the dossier are also checked. The dossier template in Annex II must be used for compiling the documents. The data according to Chapter 5, Section 9, paragraphs 1, 4 to 8 of the Rules of Procedure of the G-BA must be prepared and submitted in accordance with the requirements specified in Modules 1 to 5. According to Chapter 5 Section 9, paragraph 3, sentence 1 VerfO, the pharmaceutical company must ensure that all information on study methodology and results is made available in full for publication in the dossier in Modules 1 to 4 in accordance with paragraph 2 sentence 2.

The present submission of data by the pharmaceutical company does not comply with the requirements laid down in Chapter 5, Section 9 VerfO and proves to be inadequate and incomplete, so that it remains an obstacle to a proper assessment of the additional benefit.

The study documents that were only submitted subsequently with the written statement in the ongoing procedure were also unsuitable for an appropriate assessment of the additional benefit, taking into account the pharmaceutical company's obligation to present its case in the procedure. Subsequently, the G-BA determines in accordance with Chapter 5, Section 18, sentence 4, of the Rules of Procedure of the G-BA that an additional benefit has not been proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient olaparib.

"Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated."

In the therapeutic indication under consideration, the question for the benefit assessment was based on 2 patient groups. These differ in whether patients have received prior therapy for mCRPC or not:

a) Adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC

b) Adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated and who have received prior therapy for mCRPC

On a)

The appropriate comparator therapy includes abiraterone acetate in combination with prednisone or prednisolone, enzalutamide and olaparib according to their respective authorisation status, as well as best supportive care for patients with reduced general condition.

For the benefit assessment, the pharmaceutical company submitted data from the PROpel study. In this randomised, controlled, double-blind phase III study, patients with untreated mCRPC were randomised in a 1:1 ratio to the treatment arm (olaparib in combination with

abiraterone and prednisone or prednisolone) and the control arm (abiraterone in combination with prednisone or prednisolone). The assessment is based on the 3rd data cut-off of the PROpel study from 12 October 2022, which had been requested by the European Medicines Agency (EMA).

For several endpoints, there is consistently an effect modification by the characteristic "BRCA mutational status". Therefore, a separate assessment of the additional benefit was made for patients with BRCA mutation and patients without BRCA mutation (BRCA wild type):

a) Adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC

   a1) Adults with BRCA mutation

   a2) Adults without BRCA mutation (BRCA wild type)

On a1)

In the mortality endpoint category, there is a very clear advantage in favour of olaparib in combination with abiraterone acetate and prednisone or prednisolone.

In the endpoint categories of morbidity and health-related quality of life, there are clear advantages of olaparib in combination with abiraterone acetate and prednisone or prednisolone.

The results on side effects predominantly show disadvantages.

As a result, the G-BA identifies a considerable additional benefit of olaparib in combination with abiraterone acetate and prednisone or prednisolone compared to abiraterone acetate in combination with prednisone or prednisolone for patients with untreated mCRPC and BRCA mutation.

In particular, due to the uncertainty of the extent to which chemotherapy was not clinically indicated for all patients in the PROpel study, there is a hint for an additional benefit with regard to the significance of the evidence.

On a2)

In the endpoint categories of mortality, morbidity and health-related quality of life, there are no statistically significant differences.

In the endpoint category of side effects, there are predominantly disadvantages of olaparib in combination with abiraterone acetate and prednisone or prednisolone.

The conclusion is that an additional benefit of olaparib in combination with abiraterone acetate and prednisone or prednisolone compared to abiraterone acetate in combination with prednisone or prednisolone for patients with untreated mCRPC and no BRCA mutation is unproven.

On b)

The appropriate comparator therapy comprises a patient-individual choice of abiraterone acetate in combination with prednisone or prednisolone, enzalutamide and olaparib, each according to their authorisation status, taking into account prior therapy/ therapies and BRCA mutational status.

No data are available to allow an assessment of the additional benefit. An additional benefit is therefore not proven. Study 8, which is relevant for the benefit assessment, was not cited

by the pharmaceutical company in the benefit assessment dossier. The study documents were submitted subsequently during the written statement procedure, but the data were not processed according to the module template.

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 of the pharmaceutical company on the upper limit. In principle, these seem plausible.

The information on the lower limit is based on information provided by IQWiG, as the information provided by the pharmaceutical company is subject to uncertainties, which are explained below with the main reasons.

On the one hand, it is unclear whether the documentation of metastases with the indicated ICD codes (C77, C78, C79) is complete, and on the other, it is questionable whether all relevant patients with castration-resistant disease were identified for conventional ADT through the underlying period of 2-3 years.

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: 22 June 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 as well as specialists in urology and further doctors from other professional groups 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.

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 June 2023).

Treatment period:

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.

a) Adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC

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 + abiraterone acetate + prednisone or prednisolone + GnRH analogues				
Olaparib	Continuously, 2 x daily	365	1	365.0
Abiraterone acetate	Continuously, 1 x daily	365	1	365.0
Prednisone or Prednisolone	Continuously, 1 x daily	365	1	365.0
GnRH analogues				
Buserelin	Continuously, every 3 months	4	1	4.0
Degarelix	Continuously, 1 x monthly	12	1	12.0
Goserelin	Continuously, every 3 months	4	1	4.0
Leuprorelin	Continuously, every 3 months	4	1	4.0
Triptorelin	Continuously, every 6 months	2	1	2.0
Appropriate comparator therapy				
Abiraterone acetate + prednisone or prednisolone + GnRH analogues				
Abiraterone acetate	Continuously, 1 x daily	365	1	365.0
Prednisone or Prednisolone	Continuously, 1 x daily	365	1	365.0
GnRH analogues				
Buserelin	Continuously, every 3 months	4	1	4.0
Degarelix	Continuously, 1 x monthly	12	1	12.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Goserelin	Continuously, every 3 months	4	1	4.0
Leuprorelin	Continuously, every 3 months	4	1	4.0
Triptorelin	Continuously, every 6 months	2	1	2.0
Enzalutamide + GnRH analogues				
Enzalutamide	Continuously, 1 x daily	365	1	365.0
GnRH analogues				
Buserelin	Continuously, every 3 months	4	1	4.0
Degarelix	Continuously, 1 x monthly	12	1	12.0
Goserelin	Continuously, every 3 months	4	1	4.0
Leuprorelin	Continuously, every 3 months	4	1	4.0
Triptorelin	Continuously, every 6 months	2	1	2.0
Olaparib monotherapy + GnRH analogues				
Olaparib	Continuously, 2 x daily	365	1	365.0
GnRH analogues				
Buserelin	Continuously, every 3 months	4	1	4.0
Degarelix	Continuously, 1 x monthly	12	1	12.0
Goserelin	Continuously, every 3 months	4	1	4.0
Leuprorelin	Continuously, every 3 months	4	1	4.0
Triptorelin	Continuously, every 6 months	2	1	2.0
Best supportive care				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Best supportive care [3]	Different from patient to patient			

b) Adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated and who have received prior therapy for mCRPC

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 + abiraterone acetate + prednisone or prednisolone + GnRH analogues				
Olaparib	Continuously, 2 x daily	365	1	365.0
Abiraterone acetate	Continuously, 1 x daily	365	1	365.0
Prednisone or Prednisolone	Continuously, 1 x daily	365	1	365.0
GnRH analogues				
Buserelin	Continuously, every 3 months	4	1	4.0
Degarelix	Continuously, 1 x monthly	12	1	12.0
Goserelin	Continuously, every 3 months	4	1	4.0
Leuprorelin	Continuously, every 3 months	4	1	4.0
Triptorelin	Continuously, every 6 months	2	1	2.0
Appropriate comparator therapy				
Abiraterone acetate + prednisone or prednisolone + GnRH analogues				

3 When comparing olaparib in combination with abiraterone acetate and prednisone/ prednisolone versus best supportive care, the costs of best supportive care must also be additionally considered for the medicinal product assessed.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Abiraterone acetate	Continuously, 1 x daily	365	1	365.0
Prednisone or Prednisolone	Continuously, 1 x daily	365	1	365.0
GnRH analogues				
Buserelin	Continuously, every 3 months	4	1	4.0
Degarelix	Continuously, 1 x monthly	12	1	12.0
Goserelin	Continuously, every 3 months	4	1	4.0
Leuprorelin	Continuously, every 3 months	4	1	4.0
Triptorelin	Continuously, every 6 months	2	1	2.0
Enzalutamide + GnRH analogues				
Enzalutamide	Continuously, 1 x daily	365	1	365.0
GnRH analogues				
Buserelin	Continuously, every 3 months	4	1	4.0
Degarelix	Continuously, 1 x monthly	12	1	12.0
Goserelin	Continuously, every 3 months	4	1	4.0
Leuprorelin	Continuously, every 3 months	4	1	4.0
Triptorelin	Continuously, every 6 months	2	1	2.0
Olaparib monotherapy + GnRH analogues				
Olaparib	Continuously, 2 x daily	365	1	365.0
GnRH analogues				
Buserelin	Continuously, every 3 months	4	1	4.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Degarelix	Continuously, 1 x monthly	12	1	12.0
Goserelin	Continuously, every 3 months	4	1	4.0
Leuprorelin	Continuously, every 3 months	4	1	4.0
Triptorelin	Continuously, every 6 months	2	1	2.0

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.

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

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

a) Adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC

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 + abiraterone acetate + prednisone or prednisolone + GnRH analogues					
Olaparib	300 mg	600 mg	4 x 150 mg	365.0	1,460 x 150 mg
Abiraterone acetate	1,000 mg	1,000 mg	4 x 250 mg	365.0	1,460 x 250 mg
Prednisone or Prednisolone	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
GnRH analogues					
Buserelin	9.45 mg	9.45 mg	9.45 mg	4.0	4 x 9.45 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12 x 80 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2 x 22.5 mg
Appropriate comparator therapy					
Abiraterone acetate + prednisone or prednisolone + GnRH analogues					
Abiraterone acetate	1,000 mg	1,000 mg	4 x 250 mg	365.0	1,460 x 250 mg
Prednisone or Prednisolone	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
GnRH analogues					
Buserelin	9.45 mg	9.45 mg	9.45 mg	4.0	4 x 9.45 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12 x 80 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2 x 22.5 mg
Enzalutamide + GnRH analogues					
Enzalutamide	160 mg	160 mg	4 x 40 mg	365.0	1,460 x 40 mg
GnRH analogues					
Buserelin	9.45 mg	9.45 mg	9.45 mg	4.0	4 x 9.45 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12 x 80 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2 x 22.5 mg
Olaparib monotherapy + GnRH analogues					
Olaparib	300 mg	600 mg	4 x 150 mg	365.0	1,460 x 150 mg
GnRH analogues					
Buserelin	9.45 mg	9.45 mg	9.45 mg	4.0	4 x 9.45 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12 x 80 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2 x 22.5 mg
Best supportive care					
Best supportive care	Different from patient to patient				

b) Adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated and who have received prior therapy for mCRPC

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 + abiraterone acetate + prednisone or prednisolone + GnRH analogues					
Olaparib	300 mg	600 mg	4 x 150 mg	365.0	1,460 x 150 mg
Abiraterone acetate	1,000 mg	1,000 mg	4 x 250 mg	365.0	1,460 x 250 mg
Prednisone or Prednisolone	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
GnRH analogues					
Buserelin	9.45 mg	9.45 mg	9.45 mg	4.0	4 x 9.45 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12 x 80 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2 x 22.5 mg
Appropriate comparator therapy					
Abiraterone acetate + prednisone or prednisolone + GnRH analogues					
Abiraterone acetate	1,000 mg	1,000 mg	4 x 250 mg	365.0	1,460 x 250 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Prednisone or Prednisolone	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
GnRH analogues					
Buserelin	9.45 mg	9.45 mg	9.45 mg	4.0	4 x 9.45 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12 x 80 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2 x 22.5 mg
Enzalutamide + GnRH analogues					
Enzalutamide	160 mg	160 mg	4 x 40 mg	365.0	1,460 x 40 mg
GnRH analogues					
Buserelin	9.45 mg	9.45 mg	9.45 mg	4.0	4 x 9.45 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12 x 80 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2 x 22.5 mg
Olaparib monotherapy + GnRH analogues					
Olaparib	300 mg	600 mg	4 x 150 mg	365.0	1,460 x 150 mg
GnRH analogues					
Buserelin	9.45 mg	9.45 mg	9.45 mg	4.0	4 x 9.45 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12 x 80 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2 x 22.5 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 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.

a) Adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC

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 + abiraterone acetate + prednisone or prednisolone + GnRH analogues					
Olaparib 150 mg	112 FCT	€ 4,945.66	€ 2.00	€ 478.56	€ 4,465.10
Abiraterone acetate 250 mg	120 FCT	€ 137.72	€ 2.00	€ 16.00	€ 119.72
Prednisone[4] 10 mg	100 TAB	€ 21.19	€ 2.00	€ 0.78	€ 18.41
Prednisolone[4] 10 mg	100 TAB	€ 17.78	€ 2.00	€ 0.51	€ 15.27
GnRH analogues					
Buserelin 9.45 mg	2 PS	€ 1,028.11	€ 2.00	€ 96.51	€ 929.60
Degarelix 80 mg	3 PSS	€ 591.85	€ 2.00	€ 55.10	€ 534.75
Goserelin 10.8 mg	2 IMP	€ 1,013.52	€ 2.00	€ 95.13	€ 916.39
Leuprorelin 11.25 mg	2 IMP	€ 730.74	€ 2.00	€ 86.93	€ 641.81
Triptorelin 22.5 mg	1 TSS	€ 1,006.38	€ 2.00	€ 94.45	€ 909.93
Appropriate comparator therapy					
Abiraterone acetate + prednisone or prednisolone + GnRH analogues					
Abiraterone acetate 250 mg	120 FCT	€ 137.72	€ 2.00	€ 16.00	€ 119.72
Prednisone[4] 10 mg	100 TAB	€ 21.19	€ 2.00	€ 0.78	€ 18.41
Prednisolone[4] 10 mg	100 TAB	€ 17.78	€ 2.00	€ 0.51	€ 15.27
GnRH analogues					
Buserelin 9.45 mg	2 PS	€ 1,028.11	€ 2.00	€ 96.51	€ 929.60
Degarelix 80 mg	3 PSS	€ 591.85	€ 2.00	€ 55.10	€ 534.75
Goserelin 10.8 mg	2 IMP	€ 1,013.52	€ 2.00	€ 95.13	€ 916.39
Leuprorelin 11.25 mg	2 IMP	€ 730.74	€ 2.00	€ 86.93	€ 641.81
Triptorelin 22.5 mg	1 DSS	€ 1,006.38	€ 2.00	€ 94.45	€ 909.93
Enzalutamide + GnRH analogues					
Enzalutamide 40 mg	112 FCT	€ 3,193.29	€ 2.00	€ 127.91	€ 3,063.38
GnRH analogues					
Buserelin 9.45 mg	2 PS	€ 1,028.11	€ 2.00	€ 96.51	€ 929.60

[4] Fixed reimbursement rate

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
Degarelix 80 mg	3 PSS	€ 591.85	€ 2.00	€ 55.10	€ 534.75
Goserelin 10.8 mg	2 IMP	€ 1,013.52	€ 2.00	€ 95.13	€ 916.39
Leuprorelin 11.25 mg	2 IMP	€ 730.74	€ 2.00	€ 86.93	€ 641.81
Triptorelin 22.5 mg	1 DSS	€ 1,006.38	€ 2.00	€ 94.45	€ 909.93
Olaparib monotherapy + GnRH analogues					
Olaparib 150 mg	112 FCT	€ 4,945.66	€ 2.00	€ 478.56	€ 4,465.10
GnRH analogues					
Buserelin 9.45 mg	2 PS	€ 1,028.11	€ 2.00	€ 96.51	€ 929.60
Degarelix 80 mg	3 PSS	€ 591.85	€ 2.00	€ 55.10	€ 534.75
Goserelin 10.8 mg	2 IMP	€ 1,013.52	€ 2.00	€ 95.13	€ 916.39
Leuprorelin 11.25 mg	2 IMP	€ 730.74	€ 2.00	€ 86.93	€ 641.81
Triptorelin 22.5 mg	1 DSS	€ 1,006.38	€ 2.00	€ 94.45	€ 909.93
Abbreviations: PS = prefilled syringes; FCT = film-coated tablets; IMP = implant; PSI = powder and solvent for solution for injection; TAB = tablets; DSS = dry substance with solvent					

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b) Adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated and who have received prior therapy for mCRPC

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 + abiraterone acetate + prednisone or prednisolone + GnRH analogues					
Olaparib 150 mg	112 FCT	€ 4,945.66	€ 2.00	€ 478.56	€ 4,465.10
Abiraterone acetate 250 mg	120 FCT	€ 137.72	€ 2.00	€ 16.00	€ 119.72
Prednisone[4] 10 mg	100 TAB	€ 21.19	€ 2.00	€ 0.78	€ 18.41
Prednisolone[4] 10 mg	100 TAB	€ 17.78	€ 2.00	€ 0.51	€ 15.27
GnRH analogues					
Buserelin 9.45 mg	2 PS	€ 1,028.11	€ 2.00	€ 96.51	€ 929.60
Degarelix 80 mg	3 PSS	€ 591.85	€ 2.00	€ 55.10	€ 534.75
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Triptorelin 22.5 mg	1 DSS	€ 1,006.38	€ 2.00	€ 94.45	€ 909.93

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
Appropriate comparator therapy					
Abiraterone acetate + prednisone or prednisolone + GnRH analogues					
Abiraterone acetate 250 mg	120 FCT	€ 137.72	€ 2.00	€ 16.00	€ 119.72
Prednisone[4] 10 mg	100 TAB	€ 21.19	€ 2.00	€ 0.78	€ 18.41
Prednisolone[4] 10 mg	100 TAB	€ 17.78	€ 2.00	€ 0.51	€ 15.27
GnRH analogues					
Buserelin 9.45 mg	2 PS	€ 1,028.11	€ 2.00	€ 96.51	€ 929.60
Degarelix 80 mg	3 PSS	€ 591.85	€ 2.00	€ 55.10	€ 534.75
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Enzalutamide + GnRH analogues					
Enzalutamide 40 mg	112 FCT	€ 3,193.29	€ 2.00	€ 127.91	€ 3,063.38
GnRH analogues					
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Buserelin 9.45 mg	2 PS	€ 1,028.11	€ 2.00	€ 96.51	€ 929.60
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Triptorelin 22.5 mg	1 DSS	€ 1,006.38	€ 2.00	€ 94.45	€ 909.93
Abbreviations: PS = prefilled syringes; FCT = film-coated tablets; IMP = implant; PSI = powder and solvent for solution for injection; TAB = tablets; DSS = dry substance with solvent					

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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.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

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 Olaparib

According to Section 35a, paragraph 3, sentence 4, the G-BA designates 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.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

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 29 March 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 24 January 2023.

On 13 January 2023, 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 16 January 2023 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 12 April 2023, and the written statement procedure was initiated with publication on the G-BA website on 17 April 2023. The deadline for submitting statements was 8 May 2023.

The oral hearing was held on 22 May 2023.

By letter dated 23 May 2023, the IQWiG was commissioned with a supplementary assessment. The addenda prepared by the IQWiG were submitted to the G-BA on 15 June 2023 and 16 June 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 27 June 2023, and the proposed resolution was approved.

At its session on 6 July 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	29 March 2022	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	24 January 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	15 May 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	22 May 2023 23 May 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	30 May 2023 13 June 2023 20 June 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	27 June 2023	Concluding discussion of the draft resolution
Plenum	6 July 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 6 July 2023

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

Prof. Hecken