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)
Talazoparib in combination with enzalutamide (new therapeutic indication: prostate cancer, metastatic, castration-resistant, in combination with enzalutamide)

of 15 August 2024

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 all 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 talazoparib (Talzenna) was listed for the first time on 1 June 2020 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 5 January 2024, talazoparib received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334 from 12.12.2008, sentence 7).

On 2 February 2024, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 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 talazoparib with the new therapeutic indication

"Talzenna is indicated in combination with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated".

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 May 2024 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

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

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 Talazoparib in combination with enzalutamide (Talzenna) in accordance with the product information

Talzenna is indicated in combination with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated.

Therapeutic indication of the resolution (resolution of 15 August 2024):

"see 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 talazoparib in combination with enzalutamide:

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

– 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 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

– olaparib in combination with abiraterone acetate and prednisone or prednisolone (only for patients with BRCA mutations and for patients without BRCA mutations with symptomatic disease progression)

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

Appropriate comparator therapy for talazoparib in combination with enzalutamide:

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),
- olaparib in combination with abiraterone acetate and prednisone or prednisolone and
- 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)

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

<u>Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):</u>

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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

on 1. Medicinal products with the active ingredients bicalutamide, cyproterone acetate, flutamide, degarelix, buserelin, goserelin, leuprorelin, triptorelin, enzalutamide, abiraterone acetate, radium-223-dichloride, olaparib, niraparib and lutetium (177Lu) vipivotide tetraxetan are approved in the present therapeutic indication.

on 2. A radiotherapy is generally considered as a non-medicinal treatment in the present therapeutic indication. Radiotherapy is a potential patient-individual therapy option for all patients and is mainly used for palliative symptom control, which is why it was not

included in the appropriate comparator therapy. This does not affect the use of radiotherapy as a potential add-on therapy option.

on 3. The following resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available:

- niraparib (combination therapy), resolution of 2 May 2024
- olaparib (combination therapy), resolution of 06.07.2023
- lutetium (177Lu) vipivotide tetraxetan, resolution of 06.07.2023
- olaparib (monotherapy), resolution of 03.06.2021
- radium-223-dichloride, resolution of 17.10.2019
- enzalutamide, resolution of 18.06.2015
- enzalutamide, resolution of 20.02.2014
- abiraterone acetate, resolution of 04.07.2013
- abiraterone acetate, resolution of 29.03.2012

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 therapeutic indication according to Section 35a, paragraph 7 SGB V. There is a joint written statement from the German Society for Haematology and Medical Oncology (DGHO) and the German Society for Urology (DGU).

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

Against the background that the patients are treated with talazoparib in combination with enzalutamide, it is 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 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)) for the question of benefit assessment.

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 talazoparib in combination with enzalutamide in the target population has been made against chemotherapy. A chemotherapy is therefore not considered to be an appropriate comparator therapy in the present case.

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

The guidelines unanimously recommend the active ingredients abiraterone acetate in combination with prednisone or prednisolone, enzalutamide and docetaxel in combination with prednisone or prednisolone for the initial treatment of mCRPC. However, chemotherapy with docetaxel is not an option for the reason mentioned above. 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.

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.

However, the present therapeutic indication of talazoparib in combination with enzalutamide also includes patients with symptomatic disease progression. However, guidelines recommend abiraterone acetate in combination with prednisone or prednisolone and enzalutamide, regardless of whether the patient is asymptomatic, mildly symptomatic or symptomatic.

Moreover, olaparib in combination with abiraterone acetate and prednisone or prednisolone is another approved treatment option in the present therapeutic indication for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated. In the benefit assessment (resolution of 06.07.2023), a hint for a considerable additional benefit compared with abiraterone acetate in combination with prednisone or prednisolone was identified for adults with mCRPC for whom chemotherapy is not clinically indicated, who have not received any prior therapy for mCRPC and who have a BRCA mutation. However, no additional benefit was identified for adults with mCRPC for whom chemotherapy is not clinically indicated, who have not received prior therapy for mCRPC and who do not have a BRCA mutation (BRCA wild type).

Overall, it cannot be concluded from the available evidence that the off-label use of abiraterone acetate in combination with prednisone or prednisolone and of enzalutamide in symptomatic patients is generally preferable to the medicinal products approved in the therapeutic indication, in particular to olaparib in combination with abiraterone acetate and prednisone or prednisolone, according to the generally recognised state of medical knowledge. The prerequisites for determining the off-label use of abiraterone acetate in combination with prednisone or prednisolone and enzalutamide as an appropriate comparator therapy for symptomatic patients by way of exception in accordance with Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) are therefore not met.

In addition, niraparib in combination with abiraterone acetate and prednisone or prednisolone is a new treatment option for patients with BRCA1/2 mutations (germline

and/or somatic) for whom chemotherapy is not clinically indicated. This combination of active ingredients was approved on 19.04.2023 and only recently subjected to benefit assessment (resolution of 02.05.2024). In the process, a hint for a considerable additional benefit over abiraterone acetate in combination with prednisone or prednisolone was identified for patients with mCRPC and BRCA1/2 mutation for whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC. Based on the generally accepted state of medical knowledge, niraparib in combination with abiraterone acetate and prednisone or prednisolone is not included in the appropriate comparator therapy for the present resolution.

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).

In the overall assessment, the G-BA therefore determined abiraterone acetate in combination with prednisone or prednisolone, enzalutamide, olaparib as monotherapy or olaparib in combination with abiraterone acetate and prednisone or prednisolone as appropriate comparator therapy, taking into account the marketing authorisations presented. The appropriate comparator therapy determined here includes several therapy options. In this context, individual therapy options 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.

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

In this regard, abiraterone acetate in combination with prednisone or prednisolone is approved for patients whose disease is progressive during or after docetaxel-containing chemotherapy. By resolution of 29.03.2012, 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 docetaxel-containing chemotherapy and for whom renewed treatment with docetaxel is no longer an option; for patients who are progressive during or after docetaxel-containing chemotherapy but are still eligible for docetaxel-containing chemotherapy, the additional benefit is considered not proven, as the necessary evidence was not submitted in full. 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.

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).

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. 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 cabazitaxel is not considered to be an appropriate comparator therapy in view of the present therapeutic indication.

For the likewise approved combination of olaparib, abiraterone acetate and prednisone or prednisolone, no additional benefit compared to patient-individual therapy was identified by resolution of 06.07.2023 for adults with mCRPC for whom chemotherapy is not clinically indicated and who have already received prior therapy for mCRPC. Olaparib in combination with abiraterone acetate and prednisone or prednisolone is approved regardless of prior therapy for mCRPC and the presence of a BRCA1/2 mutation. Particularly in view of this authorisation status, olaparib in combination with abiraterone acetate and prednisone or prednisolone currently represents a treatment option in the context of patient-individual therapy for patients without a BRCA1/2 mutation with prior NHA therapy for mCRPC.

In addition, niraparib in combination with abiraterone acetate and prednisone or prednisolone is a new treatment option for patients with BRCA1/2 mutations (germline and/or somatic) for whom chemotherapy is not clinically indicated. This combination of active ingredients was approved on 19.04.2023 and only recently subjected to benefit assessment (resolution of 02.05.2024). In the process, no additional benefit was identified compared to patient-individual therapy for adults with mCRPC with a BRCA1/2 mutation for whom chemotherapy is not clinically indicated and who have already received prior therapy for mCRPC. Based on the generally accepted state of medical knowledge, niraparib in combination with abiraterone acetate and prednisone or prednisolone is not included in the appropriate comparator therapy for the present resolution.

In addition, lutetium (177Lu) vipivotide tetraxetan is another approved treatment option. The marketing authorisation exists in combination with androgen deprivation therapy (ADT) with or without androgen receptor (AR) pathway inhibition for the treatment of adult patients with progressive prostate-specific membrane antigen (PSMA)-positive mCRPC who have been treated with prior AR pathway inhibition and taxane-based chemotherapy. In the benefit assessment, an indication of a considerable additional benefit was found for adults with PSMA-positive mCRPC after previous treatment with ARDT (androgen receptor-directed therapy) and taxane-containing chemotherapy, for whom abiraterone in combination with prednisone or prednisolone, enzalutamide or best supportive care is the appropriate patient-individual therapy. However, no additional benefit was identified for adults with PSMA-positive mCRPC after prior treatment with ARDT and taxane-containing chemotherapy, for whom cabazitaxel or olaparib (as monotherapy) is the appropriate patient-individual therapy (resolution of 06.07.2023). However, it should be noted that this benefit assessment was based on the treatment setting of a third-line therapy after previous taxane-based chemotherapy and inhibition of the AR signalling pathway, and thus, on an indication that differed from the present treatment setting with regard to the prior therapy. Lutetium (177Lu) vipivotide tetraxetan is not included in the 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 identifies a patient-individual therapy, selecting abiraterone acetate in combination with prednisone or prednisolone, enzalutamide, olaparib as monotherapy and olaparib in combination with abiraterone acetate and prednisone or prednisolone as an appropriate comparator therapy, taking into account the previous therapy/ therapies and the BRCA1/2 mutational status as well as the presented marketing authorisations.

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.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of talazoparib in combination with enzalutamide is assessed as follows:

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

<u>a1) Adults without HRR deficiency</u>

Hint for a lesser benefit.

a2) Adults with HRR deficiency

An additional benefit is not proven.

Justification:

To demonstrate an additional benefit of talazoparib in combination with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC, the pharmaceutical company presented the results of the FDA data cut-off from 28 March 2023 of the second part of the ongoing two-part TALAPRO-2 study, which has been conducted since August 2017 at 287 study sites, particularly in Europe and North and South America.

Part 2 of the TALAPRO-2 study is a randomised, controlled, double-blind phase III study, in whose part 2 relevant for the benefit assessment, talazoparib in combination with enzalutamide is compared with enzalutamide.

A total of 1,106 adult patients with mCRPC in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC were enrolled in the study.

Patients should be in good general condition at the time of enrolment in the study, corresponding to an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 or 1, and be asymptomatic or mildly symptomatic (surveyed using the Brief Pain Inventory-Short Form [BPI-SF] item 3 [worst pain] < 4). Treatment with talazoparib in combination with enzalutamide or enzalutamide was randomised in a 1:1 ratio, stratified according to the factors presence of HRR deficiency (yes/ no or unclear) and previous therapy with a novel hormonal substance or taxane-containing chemotherapy for hormone-sensitive prostate cancer (yes/ no).

Relevance of the cohorts of the TALAPRO-2 study

Part 2 of the TALAPRO-2 study, which is relevant for the benefit assessment, comprises the following 3 cohorts:

- Cohort 1: Enrolment in the study was independent of the presence of homologous recombination repair (HRR) deficiency. 805 patients, 402 patients in the talazoparib + enzalutamide arm and 403 patients in the enzalutamide arm were enrolled in cohort 1. According to the study report, 169 (21%) patients in cohort 1 have HRR deficiency, 426 (53%) have no HRR deficiency and the HRR gene mutational status is unknown in 210 (26%) patients.
- Cohort 2: A total of 399 patients with at least one HRR deficiency; 200 patients in the talazoparib + enzalutamide arm and 199 patients in the enzalutamide arm were enrolled in cohort 2. Cohort 2 comprises 169 patients with HRR mutation who were already randomised in cohort 1 and thus also evaluated in cohort 1. In addition, a further 230 patients with HRR mutations were recruited exclusively for cohort 2. This results in an overlap of 169 patients who are included in both cohort 1 and cohort 2.
- Cohort 3 (Chinese extension cohort): The enrolment took place exclusively in China, irrespective of the presence of HRR deficiency, in order to fulfil requirements for the Chinese regulatory authorities. A total of 125 patients, 63 patients in the talazoparib + enzalutamide arm and 62 patients in the enzalutamide arm were enrolled. The Chinese extension cohort comprises 54 Chinese patients already randomised in cohort 1. In addition, a further 71 patients were enrolled in China exclusively for the Chinese

extension cohort. This results in an overlap of 54 patients who are included in both cohort 1 and the Chinese extension cohort.

In the dossier for the benefit assessment, the pharmaceutical company only used separate data from cohorts 1 and 2 and does not consider cohort 3. A joint analysis of cohorts 1 and 2 without overlap was not presented.

For the benefit assessment, the data of the non-overlapping evaluation cohorts 1 (adults without HRR deficiency) and 2 (adults with HRR deficiency) meta-analytically summarised by IQWiG are used to assess the additional benefit.

Implementation of the appropriate comparator therapy and limitation of the study population with regard to the indication for chemotherapy

The pharmaceutical company selected the comparison with enzalutamide from the alternative appropriate comparator therapies. This comparator only represents an appropriate comparator therapy for those patients whose disease progresses during or after chemotherapy with docetaxel or only for patients with asymptomatic or mildly symptomatic disease progression after failure of ADT in whom chemotherapy is not yet clinically indicated.

Talazoparib is approved in combination with enzalutamide for patients with mCRPC for whom chemotherapy is not clinically indicated. However, a lack of indication for chemotherapy was not an explicit inclusion criterion in the TALAPRO-2 study. It was only specified that only asymptomatic or mildly symptomatic patients, operationalised as BPI-SF item 3 score at baseline ≤ 3, were to be enrolled.

The study also enrolled patients with visceral metastases, for whom chemotherapy may be a more suitable treatment option, particularly if no chemotherapy has been given at an earlier stage of the disease. However, no data are available on the number of patients with visceral metastases who have not previously received chemotherapy.

Furthermore, it remains unclear whether further chemotherapy (especially with cabazitaxel) would have been clinically indicated for the patients with previous taxane-containing chemotherapy.

This leaves uncertainty as to whether patients for whom chemotherapy would have been clinically indicated were also enrolled in the study.

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

Analysis across endpoints

In the subgroup analyses on the characteristic "HRR gene mutational status", significantly different effects depending on the "HRR gene mutational status" were shown for each of the endpoints of symptomatology ("pain" and "symptoms of the urinary tract" surveyed using the EORTC QLQ-C30), health-related quality of life ("global health status", "physical functioning" and "role functioning" surveyed using the EORTC QLQ-C30) and specific AEs (dizziness).

Thus, this effect modification of the characteristic "HRR gene 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 HRR deficiency and without HRR deficiency on the basis of the effect modification that occurred with regard to the characteristic "HRR gene mutational status".

Mortality

The overall survival was operationalised in the TALAPRO-2 study as the time from randomisation to death from any cause.

In the meta-analysis, there was no statistically significant difference between the treatment groups.

When looking at the results in adults without HRR deficiency, there was also no statistically significant difference between the treatment groups. For adults with HRR deficiency, the results show a statistically significant difference between the treatment groups in favour of talazoparib, but without a statistically significant interaction test compared to the subgroup of adults without HRR deficiency. Against this background, no separate derivation of an additional benefit is made.

Morbidity

Progression-free survival

In the TALAPRO-2 study, progression-free survival was defined as the time between randomisation and the time of radiologically confirmed disease progression according to the RECIST (*Response Evaluation Criteria In Solid Tumours*, version 1.1) criteria version 1.1 or death from any cause. Disease progression was assessed by a blinded independent central review (BICR) committee in soft tissue according to RECIST v1.1 criteria and in bone (after subsequent confirmation) according to PCWG3 guidelines.

With talazoparib in combination with enzalutamide, a statistically significant prolongation of PFS compared to enzalutamide was observed.

The present rPFS is a composite endpoint consisting of endpoints from 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 "disease progression" is collected according to RECIST 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 available data on morbidity and health-related quality of life are used to interpret the PFS results. These results are potentially relevant in the present case because radiologically disease progression may be associated to effects on morbidity and/or quality of life.

However, the prolonged PFS with talazoparib was not associated with an advantage in terms of morbidity or quality of life in the TALAPRO-2 study. It should be noted here that the corresponding endpoints were only collected up to progression and therefore only allow statements up to the time point of progression. However, robust analysis of data before and after the time of radiologically determined progression are required to assess any impact of radiologically determined progression on quality of life as well as morbidity.

In summary, the available data do not indicate that the statistically significant prolonged time of progression-free survival with talazoparib – radiologically determined disease progression according to RECIST criteria – is associated with an improvement in morbidity or health-related quality of life.

The results for the PFS endpoint are not used in the present assessment. The overall statement on the additional benefit therefore remains unaffected by the different opinions within the G-BA regarding the patient relevance of the PFS endpoint.

Symptomatic skeletal-related events

The endpoint of symptomatic skeletal-related events was operationalised in the TALAPRO-2 study as the time from randomisation to the first occurrence of one of the following events:

- Symptomatic bone fracture
- Spinal cord compression
- Surgery on the bone
- Radiotherapy on the bone

Both "surgery on the bone" and "radiotherapy on the bone" were only permitted after radiographic progression and consultation with the sponsor and were not linked to symptomatology. This approach means that differences in these two components are potentially due to earlier progression in the control arm, whereupon radiotherapy and surgery, and thus, the occurrence of events in the endpoints "surgery on the bone" and "radiotherapy on the bone" are only possible in the first place. The results on these endpoints are therefore not interpretable, so that the composite endpoint cannot be used for the benefit assessment in the present operationalisation.

The individual components "symptomatic bone fracture" and "spinal cord compression" of the composite endpoint are not affected by the restriction and are used as separate endpoints for the assessment.

There was no statistically significant difference between the treatment arms.

<u>Cross-endpoint assessment of patient-reported endpoints (PRO) data:</u>

In the dossier for the benefit assessment, the pharmaceutical company presented analyses of the "time to first deterioration", "time to permanent deterioration" and the mean differences at the respective observation time point for the endpoints collected in the TALAPRO-2 study using the EORTC QLQ-C30, EORTC QLQ-PR25 and BPI-SF questionnaires and the EQ-5D visual analogue scale in the categories of morbidity and health-related quality of life.

However, several uncertainties remain with regard to permanent deterioration. With regard to the lack of clarity as to how missing values after the first occurrence of deterioration (e.g. discontinuation, death) were dealt with, it emerged from the written statement procedure that these were assessed as permanently deteriorated. This approach is inadequate. Furthermore, the observation periods differed between the treatment arms in cohort 1.

For the reasons mentioned, the time to permanent deterioration is unsuitable. The responder analyses over the time to first deterioration were used for the benefit assessment.

Worst pain (BPI-SF item 3), impairment due to pain (BPI-SF item 9a-g)

In the TALAPRO-2 study, patient-reported data on pain were collected using individual items of the Brief Pain Inventory - Short Form (BPI-SF) questionnaire. During the written statement procedure, it became clear that it was not the "time to first deterioration" but the "time to first confirmed deterioration" that was evaluated. However, the pharmaceutical company did not subsequently submit evaluations on the "time to first deterioration". As a result, the available results on the "time to first confirmed deterioration" cannot be assessed.

Symptomatology (EORTC QLQ-C30 and EORTC QLQ-PR25)

Symptomatology was assessed in the TALAPRO-2 study using the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-PR25 questionnaires. The responder analyses over the time

to first deterioration for the response criterion 10 points were used for the benefit assessment.

In adults with and without HRR deficiency, there was a disadvantage of talazoparib in the symptom scale "nausea and vomiting". The symptom "nausea and vomiting" is not a typical symptom in patients with prostate cancer. In the symptom scales "fatigue", "dyspnoea" and "appetite loss", there were still statistically significant differences to the disadvantage of talazoparib in combination with enzalutamide.

In adults with HRR deficiency, there were advantages in the symptom scales "pain" and "symptoms of the urinary tract".

Health status (EQ-5D VAS)

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. The time to first deterioration of ≥ 15 points is used for the benefit assessment.

There was no statistically significant difference between the treatment arms.

Conclusion on morbidity endpoints

Taking into account the endpoints used for the present assessment, negative effects were observed in several symptom scales of the EORTC QLQ-C30 in patients with and without HRR deficiency. Thus, for patients without HRR deficiency, an overall disadvantage in the morbidity endpoint category was identified.

In patients with HRR deficiency, these negative effects are offset by positive effects in "pain" and "symptoms of the urinary tract". In the assessment, neither an advantage nor a disadvantage could be identified.

Quality of life

EORTC QLQ-C30 and EORTC QLQ-PR25

Quality of life was assessed in the TALAPRO-2 study using the functional scales of the EORTC QLQ-C30 and EORTC QLQ-PR25 questionnaires. The responder analyses over the time to first deterioration for the response criterion 10 points were used for the benefit assessment.

Adults without HRR deficiency showed statistically significant disadvantages in the functional scales "global health status", "physical functioning" and "role functioning".

In adults with HRR deficiency, there was a statistically significant advantage in the functional scale "physical functioning".

The overall assessment of the results on health-related quality of life showed moderate disadvantages of talazoparib in combination with enzalutamide compared to enzalutamide for adults without HRR deficiency. For adults with HRR deficiency, there were no overall relevant differences for the benefit assessment between the treatment groups.

Side effects

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

The meta-analysis showed statistically significant differences in the SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs to the disadvantage of talazoparib in combination with enzalutamide.

Specific AEs

In detail, the meta-analysis showed statistically significant differences in the specific AEs "infections and infestations", "anaemia" and "investigations" to the disadvantage of talazoparib in combination with enzalutamide. In patients without HRR deficiency, there was also a statistically significant disadvantage in the specific AE "dizziness".

In summary, the side effects of talazoparib in combination with enzalutamide showed disadvantages due to the increase in SAEs, severe AEs as well as therapy discontinuation due to AEs in the meta-analysis. In detail, the meta-analysis showed negative effects in the specific AEs as well as additional negative effects in detail in adults without HRR deficiency of talazoparib in combination with enzalutamide compared to enzalutamide.

Overall assessment

For the assessment of the additional benefit of talazoparib in combination with enzalutamide in patients with metastatic castration-resistant prostate cancer in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC, results on mortality, morbidity, health-related quality of life and side effects from the randomised, double-blind, multicentre, controlled TALAPRO-2 study are available. In the TALAPRO-2 study, talazoparib in combination with enzalutamide was compared with enzalutamide. The assessment is based on the FDA data cut-off of the TALAPRO-2 study from 28 March 2023.

In the sub-group analyses on the characteristic "HRR gene mutational status" for the endpoints of morbidity, health-related quality of life and side effects, there were clearly different effects depending on the "HRR gene mutational status". Thus, this effect modification of the characteristic "HRR gene mutational status" occurs consistently in several endpoints relevant for the present assessment. Due to this effect modification, a separate assessment of the additional benefit for adults with HRR deficiency and adults without HRR deficiency was conducted:

a1) Adults without HRR deficiency

In the meta-analysis, there was no statistically significant difference between the treatment groups in the endpoint of overall survival. When looking at the results in adults without HRR deficiency, there was also no statistically significant difference between the treatment groups.

With regard to symptomatology, there were disadvantages in the symptom scales "nausea and vomiting", "fatigue", "dyspnoea" and "appetite loss" of the EORTC QLQ-C30.

There were neither positive nor negative effects in the endpoints "health status" (surveyed using EQ-5D-VAS), "symptomatic bone fracture" and "spinal cord compression". The data presented on the endpoints "worst pain" and "impairment due to pain" (both surveyed using the BPI-SF) cannot be assessed.

The overall assessment of the endpoint category of morbidity resulted in an overall disadvantage of talazoparib in combination with enzalutamide compared to enzalutamide, taking into account the endpoints analysed here.

For health-related quality of life, an overall disadvantage of talazoparib in combination with enzalutamide compared to enzalutamide was observed in adults without HRR deficiency, taking into account the negative effects in the functional scales "global health status", "physical functioning" and "role functioning" of the EORTC QLQ-C30.

For the endpoint category of side effects, there were disadvantages in the severe AEs, serious AEs, therapy discontinuation due to AEs, and in detail, specific AEs.

In the overall analysis of the results, no additional benefit of talazoparib in combination with enzalutamide compared to enzalutamide could be identified for any endpoint category based on the results of the TALAPRO-2 study. On the other hand, there were disadvantages in morbidity, health-related quality of life and side effects and thus an overall clear disadvantage for treatment with talazoparib in combination with enzalutamide. Due to the existing relevant disadvantages in the simultaneous absence of positive effects, no additional benefit can be derived from the available data for talazoparib in combination with enzalutamide compared with monotherapy with enzalutamide in the treatment of adults with untreated metastatic castration-resistant prostate cancer without HRR deficiency. Rather, the G-BA follows the assessment result of IQWiG from dossier assessment A24-22 of 13 May 2024 and states in accordance with Section 5, paragraph 7, No. 6 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) that talazoparib in combination with enzalutamide in the treatment of adults with untreated metastatic castration-resistant prostate cancer without HRR deficiency has a lesser benefit compared to monotherapy with enzalutamide.

a2) Adults with HRR deficiency

In the meta-analysis, there was no statistically significant difference between the treatment groups in the endpoint of overall survival. For adults with HRR deficiency, the results show a statistically significant difference between the treatment groups in favour of talazoparib, but without a statistically significant interaction test compared to the subgroup of adults without HRR deficiency. Against this background, no separate derivation of an additional benefit is made.

With regard to symptomatology (surveyed using EORTC QLQ-C30 and -PR25), there were positive effects of therapy with talazoparib in combination with enzalutamide on the symptom scales "pain" and "symptoms of the urinary tract" and a negative effect on the symptom scale "nausea and vomiting". In addition, there were statistically significant differences to the disadvantage of talazoparib on the symptom scales "fatigue", "dyspnoea" and "appetite loss". There were neither positive nor negative effects in the endpoints "health status" (surveyed using EQ-5D VAS), "symptomatic bone fracture" and "spinal cord compression". The data presented on the endpoints "worst pain" and "impairment due to pain" (surveyed using BPI-SF) cannot be assessed.

With regard to symptomatology, the positive effects for "pain" and "symptoms of the urinary tract" are thus offset by negative effects, so that neither an advantage nor a disadvantage is derived overall.

For health-related quality of life (surveyed using EORTC QLQ-C30 and -PR25), there were no relevant differences for the benefit assessment.

For the endpoint category of side effects, there were disadvantages in the severe AEs, serious AEs, therapy discontinuation due to AEs, and in detail, specific AEs.

In the overall analysis, there were therefore only disadvantages in terms of side effects. In an assessment decision, the G-BA stated that an additional benefit is not proven for talazoparib in combination with enzalutamide compared with monotherapy with enzalutamide for the treatment of adults with untreated metastatic castration-resistant prostate cancer with HRR deficiency.

<u>Demarcation from the marketing authorisation decision</u>

In contrast to the corresponding findings of the regulatory authority on the quality, efficacy and safety of the medicinal product (cf. Section 7, paragraph 2, sentence 6 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV)), a separate assessment in the

subgroups of patients without HRR deficiency and patients with HRR deficiency is carried out in the present assessment on the basis of corresponding subgroup analyses. On the other hand, the endpoint of progression-free survival, which was decisive for the decision of the regulatory authority, is not used by the G-BA in the present assessment (see above comments on the endpoint "progression-free survival").

Thus, based on the available assessment results, there is no contradiction to the findings of the regulatory authority.

For the above reasons, it can therefore be reasonably concluded that talazoparib in combination with enzalutamide has a lesser benefit than enzalutamide for the treatment of adults with untreated metastatic castration-resistant prostate cancer without HRR deficiency.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the randomised, double-blind, multicentre controlled TALAPRO-2 study.

It is unclear whether chemotherapy was not clinically indicated for all patients in the study population. In this regard, it is unclear whether chemotherapy would have been a more suitable therapy option, particularly for patients with visceral metastases.

Due to this relevant uncertainty, a reduced reliability of data is assumed for all endpoints.

In summary, the G-BA therefore derives a “hint” for the identified additional benefit with regard to the reliability of data.

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 metastatic castration-resistant prostate cancer in whom chemotherapy is not clinically indicated and who have already received prior therapy for mCRPC, the pharmaceutical company did not present any data for the assessment of additional benefit.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient talazoparib:

“Talzenna is indicated in combination with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated.”

In this therapeutic indication, the question for the benefit assessment was based on two 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

and

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 comprises abiraterone acetate in combination with prednisone or prednisolone, enzalutamide, olaparib as monotherapy or olaparib in combination with abiraterone acetate and prednisone or prednisolone, in each case according to the authorisation status.

For the benefit assessment, the pharmaceutical company submitted data from the TALAPRO-2 study. In part 2 of this two-part randomised, controlled, double-blind phase III study, patients with metastatic castration-resistant prostate cancer in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC were randomised in a 1:1 ratio to the treatment arm (talazoparib in combination with enzalutamide) and the control arm (enzalutamide). The assessment is based on the FDA data cut-off of the TALAPRO-2 study from 28 March 2023.

For the benefit assessment, the data of the non-overlapping evaluation cohorts 1 (patients without HRR deficiency) and 2 (patients with HRR deficiency) meta-analytically summarised by IQWiG were used to assess the additional benefit.

For several endpoints, there was consistently an effect modification by the characteristic "HRR gene mutational status". Therefore, a separate assessment of the additional benefit was conducted for adults without HRR deficiency and adults with HRR deficiency:

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 without HRR deficiency

   a2) Adults with HRR deficiency

On a1)

In the endpoint category of mortality, the meta-analysis did not show any statistically significant difference between the treatment groups. When looking at the results in adults without HRR deficiency, there was also no statistically significant difference between the treatment groups.

For the endpoint categories of morbidity, health-related quality of life and side effects, only disadvantages of talazoparib in combination with enzalutamide compared with enzalutamide could be identified overall, taking into account the endpoints used in the present assessment. In the simultaneous absence of a positive effect in the endpoint category of mortality, it can therefore be reasonably concluded that talazoparib in combination with enzalutamide has lesser benefit than monotherapy with enzalutamide for the treatment of adults with untreated metastatic castration-resistant prostate cancer without HRR deficiency.

In particular, due to the uncertainty of the extent to which chemotherapy was not clinically indicated for all patients in the TALAPRO-2 study, there is a “hint” for an additional benefit with regard to the significance of the evidence.

On a2)

In the endpoint category of mortality, the meta-analysis did not show any statistically significant difference. For adults with HRR deficiency, the results show a statistically significant difference between the treatment groups in favour of talazoparib, but without a statistically significant interaction test compared to the subgroup of adults without HRR deficiency. Against this background, no separate derivation of an additional benefit is made.

The overall analysis of the results for the endpoint category of morbidity showed both positive and negative effects, so that neither an advantage nor a disadvantage in morbidity could be derived overall.

With regard to the health-related quality of life, there were no relevant differences for the benefit assessment.

For the endpoint category of side effects, disadvantages could be identified for talazoparib in combination with enzalutamide compared to enzalutamide.

Thus, there were neither advantages nor disadvantages in the endpoint categories of mortality, morbidity and health-related quality of life. In contrast, there were disadvantages in the endpoint category of side effects. In an assessment decision, the G-BA stated that an additional benefit of talazoparib in combination with enzalutamide compared to monotherapy with enzalutamide for patients with untreated mCRPC and with HRR deficiency is not proven.

On b)

The appropriate comparator therapy comprises a patient-individual selection of abiraterone acetate in combination with prednisone or prednisolone, enzalutamide, olaparib as monotherapy as well as olaparib in combination with abiraterone acetate in combination with prednisone or prednisolone, each according to the authorisation status and taking into account the previous therapy/ therapies and the BRCA1/2 mutational status.

No data are available for this patient group to allow an assessment of the additional benefit. An additional benefit is therefore not proven.

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 based its resolution on the information from the previous resolution on olaparib in combination with abiraterone acetate and prednisone or prednisolone (resolution of 06.07.2023), as the information provided by the pharmaceutical company was underestimated.

The main reason for this is that the determination of patient numbers by the pharmaceutical company in the present derivation is based on various sources. This results in greater uncertainty with regard to the transferability of the percentage values used to the starting basis.

It is also unclear how fully metastases are documented using the ICD-10-GM diagnosis codes (C77.-, C78.- C79.-) and whether the time periods used in the analysis for the development of castration resistance are sufficient to take all patients into account.

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 Talzenna (active ingredient: talazoparib in combination with enzalutamide) at the following publicly accessible link (last access: 6 August 2024):

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

Treatment with talazoparib 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 July 2024).

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				
Talazoparib + enzalutamide + GnRH analogues				
Talazoparib	Continuously,	365	1	365.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	1 x daily			
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
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
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				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
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 as 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
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

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

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				
Talazoparib + enzalutamide + GnRH analogues				
Talazoparib	Continuously, 1 x daily	365.0	1	365.0
Enzalutamide	Continuously, 1 x daily	365.0	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				
Patient-individual therapy with selection of:				
Abiraterone acetate + prednisone or prednisolone + GnRH analogues				

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 as 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,	12	1	12.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	1 x monthly			
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 + 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

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 co-morbidities) are not taken into account when calculating the annual treatment costs.

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	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Talazoparib + enzalutamide + GnRH analogues					
Talazoparib	0.5 mg	0.5 mg	2 x 0.25 mg	365.0	730 x 0.25 mg
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	1 x 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
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	1 x 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	1 x 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

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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 as 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	1 x 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 + 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	1 x 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

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	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Talazoparib + enzalutamide + GnRH analogues					
Talazoparib	0.5 mg	0.5 mg	2 x 0.25 mg	365.0	730 x 0.25 mg
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	1 x 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
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	1 x 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	1 x 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

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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 as 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	1 x 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 + 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	1 x 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. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Talazoparib 0.25 mg	30 HC	€ 1,841.63	€ 2.00	€ 101.88	€ 1,737.75
Enzalutamide 40 mg	112 FCT	€ 3,123.20	€ 2.00	€ 0.00	€ 3,121.20
Buserelin 9.45 mg	2 PS	€ 1,238.90	€ 2.00	€ 67.97	€ 1,168.93
Degarelix 80 mg	3 PSI	€ 591.88	€ 2.00	€ 32.14	€ 557.74
Goserelin 10.8 mg	2 IMP	€ 1,174.45	€ 2.00	€ 64.40	€ 1,108.05
Leuprorelin 11.25 mg	2 IMP	€ 730.78	€ 2.00	€ 86.93	€ 641.85
Triptorelin 22.5 mg	1 DSS	€ 1,137.88	€ 2.00	€ 62.37	€ 1,073.51
Appropriate comparator therapy					
Abiraterone acetate 250 mg	120 TAB	€ 137.75	€ 2.00	€ 16.00	€ 119.75
Prednisone 10 mg[2]	100 TAB	€ 21.23	€ 2.00	€ 0.00	€ 19.23
Prednisolone 10 mg[2]	100 TAB	€ 17.81	€ 2.00	€ 0.51	€ 15.30
Buserelin 9.45 mg	2 PS	€ 1,238.90	€ 2.00	€ 67.97	€ 1,168.93
Degarelix 80 mg	3 PSI	€ 591.88	€ 2.00	€ 32.14	€ 557.74
Goserelin 10.8 mg	2 IMP	€ 1,174.45	€ 2.00	€ 64.40	€ 1,108.05
Leuprorelin 11.25 mg	2 IMP	€ 730.78	€ 2.00	€ 86.93	€ 641.85
Triptorelin 22.5 mg	1 DSS	€ 1,137.88	€ 2.00	€ 62.37	€ 1,073.51
Enzalutamide 40 mg	112 FCT	€ 3,123.20	€ 2.00	€ 0.00	€ 3,121.20
Olaparib 150 mg	112 FCT	€ 4,763.36	€ 2.00	€ 268.74	€ 4,492.62
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.

[2] Fixed reimbursement rate

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 need to be taken into account.

2.5 Designation of 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 the assessed medicinal product

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.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible

concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of

medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

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

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for talazoparib (Talzenna); Talzenna 0.1 mg hard capsules, Talzenna 0.25 mg, hard capsules, Talzenna 1 mg hard capsules; last revised: July 2024

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

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for talazoparib (Talzenna); Talzenna 0.1 mg hard capsules, Talzenna 0.25 mg, hard capsules, Talzenna 1 mg hard capsules; last revised: July 2024

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 3 May 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 6 February 2024.

On 2 February 2024, the pharmaceutical company submitted a dossier for the benefit assessment of talazoparib in combination with enzalutamide to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 7 February 2024, 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 talazoparib in combination with enzalutamide.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 May 2024, and the written statement procedure was initiated with publication on the G-BA website on 15 May 2024. The deadline for submitting statements was 5 June 2024.

The oral hearing was held on 24 June 2024.

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 6 August 2024, and the proposed draft resolution was approved.

At its session on 15 August 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	3 May 2023	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	6 February 2024	New determination of the appropriate comparator therapy
Working group Section 35a	19 June 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	24 June 2024	Conduct of the oral hearing
Working group Section 35a	2 July 2024 30 July 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure

Subcommittee Medicinal products	6 August 2024	Concluding discussion of the draft resolution
Plenum	15 August 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 15 August 2024

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

Prof. Hecken