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)
Niraparib/ abiraterone acetate (prostate cancer, metastatic, castration-resistant, BRCA 1/2 mutations, chemotherapy not clinically indicated, combination with prednis(ol)one)

of 2 May 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 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 relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredients niraparib/ abiraterone acetate on 15 November 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 7 November 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 15 February 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 niraparib/ abiraterone acetate 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 niraparib/ abiraterone acetate.

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 for Niraparib/ abiraterone acetate (Akeega) according to the product information

Akeega is indicated with prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated.

Therapeutic indication of the resolution (resolution of 2 May 2024):

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) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC

Appropriate comparator therapy for niraparib/ abiraterone acetate in combination with 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 symptomatic disease after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated)

  or

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

– olaparib as monotherapy (only for patients whose disease is progressive after previous treatment that included a new hormonal agent),

or

– olaparib in combination with abiraterone acetate and prednisone or prednisolone

b) Adults with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have already received a prior therapy for mCRPC

Appropriate comparator therapy for niraparib/ abiraterone acetate in combination with 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.

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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.

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

on 1. Medicinal products with the active ingredients bicalutamide, cyproterone acetate, flutamide, degarelix, buserelin, goserelin, leuprorelin, triptorelin, enzalutamide, abiraterone acetate, radium-223-dichloride, olaparib, talazoparib 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. Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- 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
- sipuleucel-T, resolution of 19.03.2015 (EU marketing authorisation repealed)
- 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.

Against the background that the patients are treated with niraparib in combination with abiraterone acetate and prednisone or prednisolone, 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 niraparib 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 an appropriate comparator therapy in the present case.

a) Adults with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) 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 for niraparib in combination with abiraterone acetate and prednisone or prednisolone also includes patients with symptomatic disease. However, guidelines recommend abiraterone acetate in combination with prednisone or prednisolone and enzalutamide, regardless of whether the patient is asymptomatic, mildly symptomatic or symptomatic.

Olaparib in combination with abiraterone acetate and prednisone or prednisolone is another relatively new treatment option in this therapeutic indication. The marketing authorisation is for the treatment of adult patients with mCRPC for 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). However, this population is irrelevant for the present implementation of the appropriate comparator therapy, as the approved therapeutic indication of niraparib/ abiraterone acetate in combination with prednisone or prednisolone is restricted to patients with BRCA1/2 mutations (germline and/or somatic).

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 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).

The active ingredient talazoparib is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved (marketing authorisation on 05.01.2024). Based on the generally accepted state of medical knowledge, talazoparib is not determined to be an appropriate comparator therapy for the present resolution.

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) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have already received a 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 therefore not considered as an appropriate comparator therapy for adults with mCRPC and BRCA1/2 mutations (germline and/or somatic) for whom chemotherapy is not clinically indicated and who have received prior therapy for mCRPC.

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).

The therapeutic significance of lutetium (177Lu) vipivotide tetraxetan for patients with BRCA1/2 mutations (germline and/or somatic) cannot currently be conclusively assessed in the overall picture of the available evidence. Lutetium (177Lu) vipivotide tetraxetan is not determined to be an appropriate comparator therapy for the present resolution for the patient group b).

The active ingredient talazoparib is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved (marketing authorisation on 05.01.2024). Based on the generally accepted state of medical knowledge, talazoparib 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 identifies 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 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 niraparib/ abiraterone acetate is assessed as follows:

a) Adults with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC

Hint for a considerable additional benefit.

Justification:

For the benefit assessment, the pharmaceutical company submitted data from the randomised, double-blind phase III MAGNITUDE study, which compared niraparib/ abiraterone acetate in combination with prednisone or prednisolone versus placebo in combination with abiraterone acetate and prednisone or prednisolone. Patients without a previous bilateral orchiectomy should continue an existing androgen deprivation therapy (ADT) in addition to the study medication.

The study enrolled adult males with mCRPC and an ECOG-PS of 0 or 1 and an asymptomatic or mildly symptomatic condition (collected via the Brief Pain Inventory-Short Form [BPI-SF] item 3 [worst pain] ≤ 3 at baseline) who had disease progression with existing ADT by medical or surgical castration and had not yet received prior therapy at the stage of mCRPC.

The MAGNITUDE study was divided into 3 cohorts depending on the presence or absence of HRR mutations. Of the 3 cohorts, only cohort 1 is relevant for the benefit assessment, as cohort 2 exclusively enrolled patients without HRR mutation and cohort 3 is a single-arm cohort for the evaluation of the fixed combination of niraparib/ abiraterone acetate. The free combination of niraparib and abiraterone acetate used in cohort 1 is considered by the EMA to be bioequivalent to the approved fixed combination of the active ingredients. The marketing authorisation of niraparib/ abiraterone acetate in combination with prednisone or prednisolone includes only those patients with BRCA1/2 mutations (germline and/or somatic) from the group of patients with HRR mutations.

Within cohort 1, a total of 423 patients were enrolled and randomised in a 1:1 ratio to either treatment with niraparib/ abiraterone acetate in combination with prednisone or prednisolone (intervention arm; N = 212) or placebo in combination with abiraterone acetate and prednisone or prednisolone (control arm; N = 211). Randomisation was stratified according to previous taxane-containing chemotherapy (yes/ no), previous androgen receptor (AR)-directed therapy (yes/ no), bridge therapy with abiraterone acetate + P in the mCRPC stage (yes/ no) and the presence of a gene mutation (BRCA1 or BRCA2/ all other HRR mutations).

Treatment with the study medication continued until disease progression, defined by an increasing PSA level with radiological confirmation or clinical progression, unacceptable toxicity, withdrawal of informed consent by the patient, lost to follow-up or study termination.

The primary endpoint of the MAGNITUDE study is the radiologically confirmed progression-free survival (rPFS). Patient-relevant endpoints were collected in the categories of mortality, morbidity, health-related quality of life and side effects. This assessment is based on the results of the final data cut-off from 15 May 2023.

Restriction of the study population with regard to indication for chemotherapy

Niraparib/ abiraterone acetate is approved in combination with prednisone or prednisolone for patients with mCRPC and BRCA1/2 mutations for whom chemotherapy is not clinically indicated. However, a lack of indication for chemotherapy was not an explicit inclusion criterion in the MAGNITUDE study. It was only specified that only asymptomatic or mildly symptomatic patients, operationalised as BPI-SF item 3 score at baseline ≤ 3, would be

enrolled (even if 5% of patients in the control arm of the relevant sub-population had a value > 3 at baseline).

In the dossier, the pharmaceutical company presents analyses of a sub-population of patients with BRCA1/2 mutation from cohort 1 of the MAGNITUDE study for whom, in its opinion, chemotherapy was not clinically indicated. For the selection of this sub-population, it defined two criteria, following a criticism by the EMA as to whether chemotherapy could be a better therapy option than abiraterone acetate on the comparator side, particularly for the group of symptomatic patients and/or with visceral metastases who have not received prior chemotherapy in mHSPC:

- patients without prior taxane-containing chemotherapy who are mild or asymptomatic (as measured by BPI-SF item 3) and have no visceral metastases (low disease burden) and
- patients with previous taxane-containing chemotherapy (regardless of symptomatology or disease burden).

According to the information on the patients' prior therapies, the previous taxane-containing chemotherapy was docetaxel therapy for all patients. In the appropriately tailored sub-population, 92 patients remain in the intervention arm and 88 patients in the control arm.

The pharmaceutical company's approach is considered appropriate overall. However, uncertainty remains insofar as it remains unclear whether further chemotherapy would have been clinically indicated for patients with previous taxane-containing chemotherapy (especially with cabazitaxel). Detailed information on why further taxane-based chemotherapy (especially cabazitaxel) was unsuitable for patients who had previously undergone taxane-based chemotherapy is not available.

Bridge therapy with abiraterone acetate and prednisone or prednisolone

The MAGNITUDE study enrolled adult patients with mCRPC who had not yet received treatment for this stage. This did not include treatment for up to 4 months prior to randomisation with abiraterone acetate in combination with prednisone or prednisolone. The pharmaceutical company justifies this exception with the fact that testing for the HRR mutations was carried out during this period, although some of the patients would have required rapid initiation of a new therapy to control the disease due to a more aggressive course of the disease. In the relevant sub-population, 25% of patients in the intervention arm and 20% of patients in the comparator arm received bridge therapy. No information is available on how long the patients actually had to wait for the results of the HRR mutation test.

Overall, the period of up to 4 months granted until the results of the HRR test are available is considered to be disproportionately long. The potentially long duration of the test results in uncertainty regarding its transferability to the German healthcare context.

Implementation of the appropriate comparator therapy

The pharmaceutical company selects abiraterone acetate in combination with prednisone or prednisolone from the alternatives of the appropriate comparator therapy. This comparator is only appropriate for patients whose disease progresses during or after docetaxel-containing chemotherapy or only for patients with asymptomatic or mildly symptomatic disease after failure of ADT in whom chemotherapy is not yet clinically indicated.

Due to the size of the relevant sub-population, it is assumed that these two characteristics are adequately taken into account. In the relevant sub-population of the MAGNITUDE study, prior therapy with a taxane-containing chemotherapy is exclusively a pretreatment with docetaxel.

Adequate treatment of bone metastases

In this therapeutic indication, adequate concomitant treatment of bone metastases is assumed (e.g. use of bisphosphonates, denosumab, radiotherapy). However, according to the MAGNITUDE study protocol, radiotherapy was not permitted until protocol version 2. After that, palliative radiotherapy was permitted, but only in individual cases in consultation with the sponsor. Even taking into account the written statement procedure, it remains unclear whether or in how many patients this restriction has led to bone metastases not being adequately treated. However, other concomitant treatments for bone metastases (e.g. bisphosphonates and denosumab) were not restricted.

Extent and probability of the additional benefit

Mortality

For the endpoint of overall survival, there was a statistically significant difference to the advantage of niraparib/ abiraterone acetate in combination with prednisone or prednisolone compared to the control arm in the relevant sub-population of patients for whom chemotherapy was not clinically indicated. The extent of the advantage achieved in overall survival is assessed as a significant improvement.

In the subgroup analyses for the endpoint of overall survival, there was an effect modification by the characteristic "prior taxane-containing chemotherapy" (yes vs no; p = 0.029). For patients without prior taxane-containing chemotherapy, there was a statistically significant difference to the advantage of niraparib/ abiraterone acetate in combination with prednisone or prednisolone. For patients with prior taxane-containing chemotherapy, there was no difference between the treatment groups.

However, the present effect modification is based on comparatively small patient numbers in the subgroups. According to the statements made by the clinical experts in the present benefit assessment procedure, there is also no recognisable biological rationale for this effect modification.

In the overall analysis, the effect modification by the characteristic "prior taxane-containing chemotherapy" is considered inadequate to derive corresponding separate conclusions on the additional benefit.

Morbidity

Radiological progression-free survival (rPFS)

In the MAGNITUDE study, rPFS was operationalised as the time from the date of randomisation to the date of radiological progression or death, depending on which event occurred first.

For the rPFS, there was a statistically significant difference to the advantage of niraparib/ abiraterone acetate in combination with prednisone or prednisolone.

The rPFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component "mortality" was already collected as an independent endpoint in the study via the endpoint "overall survival". The morbidity component was not collected in a symptom-related manner but exclusively by means of imaging procedure (radiologically assessed disease progression according to the PCWG3 criteria or the RECIST version 1.1 criteria).

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

Symptomatic progression

The patients in the present therapeutic indication are in a palliative treatment setting. Symptom control and maintaining quality of life are therefore of particular importance. Symptomatic progression is therefore generally considered a patient-relevant event.

In the MAGNITUDE study, the endpoint of symptomatic progression was defined as the time from randomisation to the first documentation of one of the following events:

- cancer-related morbidity events (for example: fractures [symptomatic and/or pathological], spinal cord compression, urinary tract obstruction events)
- use of external radiotherapy for skeletal events
- necessity of a tumour-related orthopaedic procedure
- start of a new systemic cancer therapy due to cancer pain
- use of other cancer-related interventions (e.g. insertion of a nephrostomy, insertion of a bladder catheter, external radiotherapy or surgery for tumour symptoms that do not affect the skeleton).

The evaluations on this endpoint presented in the dossier were considered unsuitable by IQWiG in the dossier assessment, particularly as it remained unclear which events were defined as symptomatic and which events were actually included in the composite endpoint, whether all events included (in particular for the components "cancer-related morbidity events" and "use of other cancer-related interventions") are necessarily patient-relevant and how the evaluation dealt with the fact that the component "initiation of new systemic cancer therapy due to cancer pain" was only included with version 5 of the electronic data collection form and it had to be assumed accordingly that this endpoint component was not collected in the 1st year after recruitment.

In its written statement, the pharmaceutical company submitted further data and evaluations for the endpoint of symptomatic progression on the points of criticism addressed.

However, based on the list of categories included in the endpoint submitted with the statement, it remains unclear which events were actually collected. However, this would be particularly relevant for assessing the patient relevance of the components "cancer-related morbidity events" and "use of other cancer-related interventions".

For the component "cancer-related morbidity events", the pharmaceutical company also submitted information on the distribution of events in the categories of spinal cord compression, fractures (symptomatic and/or pathological), urinary tract obstruction, other urinary tract symptoms and acute kidney injury. The pharmaceutical company also addresses the uncertainty as to the extent to which patient relevance or comparability of the severity of the events directly results for all events with a sensitivity analysis in which only the events of spinal cord compression or fractures (symptomatic and/or pathological) are taken into account in this component. All events collected under urinary tract obstruction, other urinary tract symptoms or acute kidney injury are not included in this sensitivity analysis. No further information is available for the component "use of other cancer-related interventions".

The pharmaceutical company also mentions in the statement that no patient started a new systemic cancer therapy before the amended version 5 of the electronic data collection form.

The lack of collection of this component during the 1st year after recruitment therefore has no consequences in this case.

For the component "use of external radiotherapy for skeletal events", it remains unclear whether palliative radiotherapy was possible without restriction throughout the course of the study.

Despite the continuing limitations, the endpoint can be used for the benefit assessment in the overall assessment, taking into account the sensitivity analysis. However, uncertainties remain as to which events were collected in the "other cancer-related interventions" component. In addition, the operationalisation chosen by the pharmaceutical company (retrospective collection of an intervention due to symptomatology) is considered insufficient to collect the events of symptomatic progression with adequate sensitivity.

Pain (BPI-SF)

In the MAGNITUDE study, patient-reported data on pain were collected using the Brief Pain Inventory - Short Form questionnaire (BPI-SF) and several operationalisations were presented.

Worst pain

For the endpoint of worst pain, collected using item 3 of the BPI-SF, no statistically significant difference was detected between the treatment arms.

Impairment due to pain

There was also no statistically significant difference between the treatment arms for the endpoint of impairment due to pain, collected using items 9a-g of the BPI-SF.

Pain intensity

Furthermore, evaluations of the BPI-SF for items 3-6 are available for pain intensity. However, in order to avoid double counting, only the worst pain and the impairment due to pain are used for the assessment. The results for the average pain intensity are only presented additionally.

Health status (EQ-5D, visual analogue scale)

For the endpoint of health status, assessed by EQ-5D VAS, there is no statistically significant difference between the treatment arms.

Overall, there is an additional benefit of niraparib/ abiraterone acetate in combination with prednisone or prednisolone compared with abiraterone acetate in combination with prednisone or prednisolone in the endpoint category of morbidity, which results from the advantage in the endpoint of symptomatic progression. The extent of this benefit cannot be conclusively assessed due to remaining uncertainties regarding the operationalisation of the endpoint. With regard to patient-reported symptomatology, collected using the BPI-SF and EQ-5D VAS measurement instruments, there were no assessment relevant differences between the treatment arms.

<u>Quality of life</u>

Health-related quality of life data was collected in the MAGNITUDE study using the FACT-P instrument.

The FACT-P consists of the cross-tumour disease questionnaire (FACT-G) and a prostate cancer sub-scale (PCS). The FACT-G 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 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 only presented additionally.

For the total score of the FACT-P, there was no statistically significant difference between the treatment groups.

Side effects

Adverse events (AEs) in total

Nearly all patients in the MAGNITUDE study experienced an adverse event. The results for the total AEs endpoint are only presented additionally.

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

There were no statistically significant differences between the treatment arms for the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AEs.

Specific AEs

In detail, there was a statistically significant difference in the area of specific AEs to the disadvantage of niraparib/ abiraterone acetate in combination with prednisone or prednisolone with regard to the endpoint of anaemia (severe AE).

In the overall assessment of the results on side effects, there are no relevant difference for the benefit assessment between the treatment arms.

Overall assessment

For the assessment of the additional benefit of niraparib/ abiraterone acetate in combination with prednisone or prednisolone in adults with metastatic castration-resistant prostate cancer (mCRPC) and BRCA1/2 mutations (germline and/or somatic), in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC, results are available from the MAGNITUDE study for the endpoint categories of mortality, morbidity, health-related quality of life and side effects.

For the overall survival endpoint, there was a statistically significant advantage of niraparib/ abiraterone acetate in combination with prednisone or prednisolone over abiraterone acetate in combination with prednisone or prednisolone.

The subgroup analyses for the endpoint "overall survival" showed an effect modification with regard to the characteristic "prior taxane-containing chemotherapy". In its assessment of this subgroup analysis, the G-BA comes to the conclusion that the interpretation of this effect modification is fraught with relevant uncertainties. A separate assessment of the additional benefit after prior taxane-containing chemotherapy is not performed.

Niraparib/ abiraterone acetate in combination with prednisone or prednisolone results in a prolongation of overall survival compared to abiraterone acetate in combination with prednisone or prednisolone, which is assessed as a significant improvement.

In the morbidity endpoint category, there is an advantage of niraparib/ abiraterone acetate in combination with prednisone or prednisolone for the endpoint of symptomatic progression. With regard to patient-reported symptomatology, collected using the BPI-SF and EQ-5D VAS measurement instruments, there were no assessment relevant differences between the treatment arms.

Treatment with niraparib/ abiraterone acetate in combination with prednisone or prednisolone had neither positive nor negative effects on health-related quality of life.

In the overall assessment of the results on side effects, there are no relevant differences for the benefit assessment between the treatment arms. In detail, only the specific adverse events show a disadvantage for the endpoint of anaemia (severe AE).

The G-BA concluded that niraparib/ abiraterone acetate in combination with prednisone or prednisolone for the treatment of adults with mCRPC and BRCA1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC has a considerable additional benefit compared with abiraterone acetate in combination with prednisone or prednisolone.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, double-blind, placebo-controlled phase III MAGNITUDE study. The risk of bias is classified as low at study level.

With regard to the endpoint of overall survival, uncertainties arise due to the existing effect modification by the characteristic "prior taxane-containing chemotherapy".

Limitations across endpoints result from the bridging therapy with abiraterone acetate and prednisone or prednisolone permitted in the study and the length of the period of up to 4 months allowed for this until the results of the HRR test are available. The potentially disproportionately long duration of the test results in uncertainty regarding its transferability to the German healthcare context.

On the basis of the available evidence, the reliability of data is thus classified in the "hint" category.

b) Adults with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have already received a prior therapy for mCRPC

An additional benefit is not proven.

Justification:

For the treatment of adults with pretreated metastatic castration-resistant prostate cancer in whom chemotherapy is not clinically indicated, no data are available that would allow an assessment of the additional benefit.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the medicinal product Akeega with the fixed combination of active ingredients niraparib/ abiraterone acetate. The therapeutic indication assessed here is as follows:

"Akeega is indicated with prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) 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) and BRCA 1/2 mutations (germline and/or somatic) 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) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have already received a prior therapy for mCRPC

About patient group 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 randomised, double-blind, placebo-controlled phase III MAGNITUDE study, which compared niraparib/ abiraterone acetate in combination with prednisone or prednisolone versus abiraterone acetate in combination with prednisone or prednisolone.

For the endpoint of overall survival, there is a clear advantage of niraparib/ abiraterone acetate in combination with prednisone or prednisolone.

The subgroup analyses for the endpoint "overall survival" showed an effect modification with regard to the characteristic "prior taxane-containing chemotherapy". In its assessment of this subgroup analysis, the G-BA comes to the conclusion that the interpretation of this effect modification is fraught with relevant uncertainties. A separate assessment of the additional benefit after prior taxane-containing chemotherapy is not performed.

In the morbidity endpoint category, there is an advantage of niraparib/ abiraterone acetate in combination with prednisone or prednisolone for the endpoint of symptomatic progression. With regard to patient-reported symptomatology, collected using the BPI-SF and EQ-5D VAS measurement instruments, there were no assessment relevant differences between the treatment arms.

There were no relevant differences for the assessment of the health-related quality of life and side effects.

In the overall assessment, the G-BA found a considerable additional benefit.

Uncertainties remain, particularly as a result of effect modification for the endpoint of overall survival. The reliability of data of the additional benefit identified is classified in the "hint" category.

About patient group b)

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

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 pharmaceutical company's derivation of the patient numbers in the dossier is mathematically comprehensible. The information is however subject to major uncertainty.

The calculation is largely based on an analysis of data or the extraction of percentage values from the "UroCloud" registry from 2022. In particular, an underestimation can be assumed due to the high number of patients no longer actively documented in the registry. Furthermore, the transferability of the percentage value for metastatic prostate cancer taken from the UroCloud registry to the 10-year prevalence is also associated with uncertainties, as the determination of patients with prostate cancer in the baseline population of the registry analysis differs from that in the 10-year prevalence.

In view of these uncertainties, in order to enable a consistent analysis of the patient numbers, taking into account the most recent resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication in question, the information from the resolution on olaparib in combination with abiraterone acetate and prednisone or prednisolone from 06.07.2023 is used as a basis for the present resolution, taking into account a range of 11% to 18% for the percentage of patients with BRCA1/2 mutations and a value of 88.1% for the percentage of SHI-insured patients. This concerns the information on the patient numbers for patient groups a) and b) combined. However, the patient numbers for patient groups a) and b) cannot be stated separately because the percentages used by the pharmaceutical company are unsuitable for this purpose. The percentages refer to patients who started treatment before the onset of the mCRPC stage or, according to the statement of the pharmaceutical company, patients were considered to have been pretreated in the mCRPC stage if they started treatment before the mCRPC stage and continued it in the mCRPC stage. The percentage values therefore do not indicate what percentage of all patients in the mCRPC stage have already received chemotherapy or novel hormone therapy in this stage (mCRPC), regardless of the therapy in previous stages of the disease.

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 Akeega (active ingredient: niraparib/ abiraterone acetate) at the following publicly accessible link (last access: 20 March 2024):

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

Treatment with niraparib/ abiraterone acetate 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 requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 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) and BRCA 1/2 mutations (germline and/or somatic) 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				
Niraparib/ abiraterone acetate + prednisone or prednisolone + GnRH analogues				
Niraparib/ 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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
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				
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,	2	1	2.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	every 6 months			
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
Goserelin	Continuously, every 3 months	4	1	4.0
Leuprorelin	Continuously,	4	1	4.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	every 3 months			
Triptorelin	Continuously, every 6 months	2	1	2.0

b) Adults with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have already received a 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				
Niraparib/ abiraterone acetate + prednisone or prednisolone + GnRH analogues				
Niraparib/ 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				

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				

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

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.

a) Adults with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) 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					
Niraparib/ abiraterone acetate + prednisone or prednisolone + GnRH analogues					
Niraparib/ abiraterone acetate	200 mg/ 1,000 mg	200 mg/ 1,000 mg	2 x 100 mg/ 500 mg	365.0	730 x 100 mg/ 500 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
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
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
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					

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

<u>b) Adults with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have already received a prior therapy for mCRPC</u>

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					
Niraparib/ abiraterone acetate + prednisone or prednisolone + GnRH analogues					

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Niraparib/ abiraterone acetate	200 mg/ 1,000 mg	200 mg/ 1,000 mg	2 x 100 mg/ 500 mg	365.0	730 x 100 mg/ 500 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
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
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4 x 11.25 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
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

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					
Niraparib/ abiraterone acetate 100 mg/500 mg	56 FCT	€ 6,596.77	€ 2.00	€ 373.45	€ 6,221.32
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	2 PS	€ 1,114.57	€ 2.00	€ 61.08	€ 1,051.49
Degarelix	3 PSI	€ 591.88	€ 2.00	€ 32.14	€ 557.74
Goserelin	2 IMP	€ 1,174.45	€ 2.00	€ 64.40	€ 1,108.05
Leuprorelin	2 IMP	€ 730.78	€ 2.00	€ 86.93	€ 641.85
Triptorelin	1 DSS	€ 1,075.11	€ 2.00	€ 58.90	€ 1,014.21

2 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
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	2 PS	€ 1,114.57	€ 2.00	€ 61.08	€ 1,051.49
Degarelix	3 PSI	€ 591.88	€ 2.00	€ 32.14	€ 557.74
Goserelin	2 IMP	€ 1,174.45	€ 2.00	€ 64.40	€ 1,108.05
Leuprorelin	2 IMP	€ 730.78	€ 2.00	€ 86.93	€ 641.85
Triptorelin	1 DSS	€ 1,075.11	€ 2.00	€ 58.90	€ 1,014.21
Enzalutamide 40 mg	112 FCT	€ 3,123.20	€ 2.00	€ 0.00	€ 3,121.20
Olaparib 150 mg	112 FCT	€ 4,945.71	€ 2.00	€ 279.16	€ 4,664.55
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 need 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 Hilfstaxe.

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) and BRCA 1/2 mutations (germline and/or somatic) 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 niraparib/ abiraterone acetate (Akeega); Akeega® 50 mg/500 mg film-coated tablets Akeega® 100 mg/500 mg film-coated tablets; last revised: April 2023

b) Adults with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have already received a 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 niraparib/ abiraterone acetate (Akeega); Akeega® 50 mg/500 mg film-coated tablets Akeega® 100 mg/500 mg film-coated tablets; last revised: April 2023

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 22 February 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 10 October 2023.

On 7 November 2023, the pharmaceutical company submitted a dossier for the benefit assessment of niraparib/ abiraterone acetate to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 14 November 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 niraparib/ abiraterone acetate.

The dossier assessment by the IQWiG was submitted to the G-BA on 9 February 2024, and the written statement procedure was initiated with publication on the G-BA website on 15 February 2024. The deadline for submitting statements was 7 March 2024.

The oral hearing was held on 25 March 2024.

By letter dated 26 March 2024, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 11 April 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 23 April 2024, and the proposed resolution was approved.

At its session on 2 May 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	22 February 2022	Implementation of the appropriate comparator therapy
Subcommittee Medicinal products	10 October 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	20 March 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	25 March 2024	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	4 April 2024 17 April 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	23 April 2024	Concluding discussion of the draft resolution
Plenum	2 May 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 2 May 2024

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

Prof. Hecken