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) Darolutamide (new therapeutic indication: prostate cancer, metastatic, hormone-sensitive, combination with docetaxel and androgen deprivation therapy)

of 21 September 2023

Contents

1. Legal basis

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

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

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

On 27 February 2023, darolutamide 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, 12.12.2008, sentence 7).

On 24 March 2023, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient darolutamide with the new

therapeutic indication (metastatic hormone-sensitive prostate cancer; combination with docetaxel and androgen deprivation therapy) in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on the G-BA website (www.g-ba.de) on 3 July 2023, thus initiating the written statement procedure. An oral hearing was also held.

The G-BA came to a resolution on whether an additional benefit of darolutamide 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 darolutamide.

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 Darolutamide (Nubeqa) in accordance with the product information

Nubeqa is indicated for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel and androgen deprivation therapy.

Therapeutic indication of the resolution (resolution of 21.09.2023):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult males with metastatic hormone-sensitive prostate cancer (mHSPC)

Appropriate comparator therapy for darolutamide in combination with docetaxel and androgen deprivation therapy:

- conventional androgen deprivation in combination with apalutamide

or

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

- conventional androgen deprivation in combination with enzalutamide

or

- conventional androgen deprivation in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed, high-risk prostate cancer)

or

- conventional androgen deprivation in combination with docetaxel with or without prednisone or prednisolone

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, relugolix, buserelin, goserelin, leuprorelin, triptorelin, abiraterone acetate, apalutamide, enzalutamide and docetaxel are approved in the present therapeutic indication.

on 2. As a non-medicinal treatment option, an orchiectomy, in addition to the use of GnRH agonists or GnRH antagonists, is one way to implement conventional androgen deprivation (ADT).

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

- abiraterone acetate (resolution of 07.06.2018)
- apalutamide (resolution of 20.08.2020)
- enzalutamide (resolution of 19.11.2021)
- relugolix (resolution of 06.04.2023)

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.

In the present therapeutic indication, it is assumed that combination therapy - additional therapy to conventional androgen deprivation therapy (ADT) - is usually an option for the patients, taking into account any comorbidities and the general condition. In this regard, guidelines unanimously advocate therapy with apalutamide, enzalutamide or abiraterone acetate or chemotherapy with docetaxel in addition to conventional ADT. The background to these recommendations is that, compared with conventional ADT alone, relevant advantages in therapeutic benefit have been shown both by combination with docetaxel and with the other therapies mentioned.

In the recommendations, the guidelines take into account that the study populations were defined in different ways, based on metastatic pattern or Gleason score, in the approval studies for docetaxel and abiraterone acetate (plus prednisone/prednisolone). In the CHAARTED approval study for docetaxel, patients were divided by volume (*high* and *low*) with regard to tumour burden. The marketing-authorisation-related LATITUDE study of abiraterone acetate enrolled only patients who were *de novo* metastatic and had a high-risk profile. The S3 guideline, therefore, classifies patients by *high* and *low volume* as well as *high* and *low risk*.

In their written statement, the scientific-medical societies follow the categorisation of the guidelines, but note that data on patients with low tumour burden are inconsistent, and chemotherapy may be beneficial regardless of tumour burden.

In the corresponding benefit assessment on abiraterone acetate, an indication of a considerable additional benefit of combination therapy with ADT and prednisone or prednisolone compared to conventional ADT was identified for patients with newly diagnosed high-risk, metastatic prostate cancer (resolution of 07.06.2018). In the benefit assessment of apalutamide in combination with ADT, no additional benefit was identified for patients with distant metastases (M1 stage) and good general condition (0 to 1 according to ECOG / WHO or ≥ 70% according to Karnofsky index), compared to docetaxel in combination with prednisolone and ADT (resolution of 20.08.2020). Likewise, the G-BA did not identify any additional benefit of enzalutamide in combination with ADT over docetaxel in combination with prednisolone and ADT for patients with distant metastases (M1 stage) and good general condition (0 to 1 according to ECOG / WHO or ≥ 70% according to Karnofsky index) (resolution of 15.12.2021).

In the overall analysis of the available evidence, the treatment options apalutamide, enzalutamide as well as docetaxel with or without prednisone or prednisolone - each of the treatment options in combination with conventional androgen deprivation - are considered equally appropriate comparator therapies. Only for patients with newly diagnosed high-risk prostate cancer does abiraterone acetate in combination with prednisone or prednisolone and conventional androgen deprivation represent another equally suitable comparator therapy in accordance with the marketing authorisation.

In the context of the present therapeutic indication, conventional androgen deprivation therapy refers to surgical or medicinal castration by therapy with GnRH agonists or GnRH antagonists. In this regard, no additional benefit could be identified for the GnRH antagonist relugolix in any patient group (resolution of 06.04.2023).

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 darolutamide in combination with docetaxel and androgen deprivation therapy is assessed as follows:

Indication of a considerable additional benefit.

Justification:

For the benefit assessment, the pharmaceutical company submitted data from the randomised, double-blind phase III ARASENS study, which compared darolutamide in combination with docetaxel and ADT versus placebo in combination with docetaxel and ADT.

The study enrolled adult males with mHSPC and an ECOG-PS of 0 or 1 who had started ADT, either by previous orchiectomy or by use of GnRH agonists or GnRH antagonists, within 12 weeks prior to enrolment in the study.

A total of 1305 patients were enrolled and randomised in a 1:1 ratio to treatment with darolutamide in combination docetaxel and ADT (intervention arm; N = 651) or placebo in combination with docetaxel and ADT (control arm; N = 654). Randomisation was stratified by extent of disease at the start of the study (non-regional lymph node metastases only vs bone metastases with or without lymph node metastases and without visceral metastases vs visceral metastases with or without lymph node metastases or with or without bone metastases) and alkaline phosphatase concentration at the start of the study (< upper limit of normal range vs ≥ upper limit of normal range).

The treatment with darolutamide or docetaxel was carried out in compliance with the marketing authorisation. The administration of prednisone or prednisolone was possible in addition to docetaxel at the discretion of the principal investigator.

Patients were treated until disease progression, unacceptable toxicity, withdrawal of informed consent or therapy discontinuation at the physician's discretion, death or non-compliance. There were no limitations with regard to subsequent therapies.

The primary endpoint of the ARASENS study was overall survival. Other patient-relevant endpoints were assessed in the categories of morbidity and side effects. This assessment is based on the results of the data cut-off of 25.10.2021.

Extent and probability of the additional benefit

Mortality

For the endpoint of overall survival, there is a statistically significant difference to the advantage of darolutamide in combination with docetaxel and ADT compared to the control arm.
The extent of the advantage achieved in overall survival is assessed as a significant improvement.

Morbidity

Symptomatic skeletal events

The composite endpoint of symptomatic skeletal events collected in the ARASENS study is operationalised as the time from randomisation to the first documentation of one of the following components:

- external radiotherapy to alleviate skeletal symptoms,
- new symptomatic pathological bone fractures,
- occurrence of spinal cord compression,
- tumour-related orthopaedic surgical intervention.

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. The endpoint of symptomatic skeletal events in the present operationalisation is considered patient-relevant. There is a statistically significant advantage of darolutamide in combination with docetaxel and ADT over the control arm for the composite endpoint.

As only the first event within the composite endpoint of symptomatic skeletal events was recorded, an effect estimate for the individual components of the endpoint cannot be meaningfully interpreted.

Pain (BPI-SF)

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

Worst pain

For the endpoint of worst pain, assessed by item 3 of the BPI-SF, the time-to-event analysis shows a statistically significant difference to the advantage of darolutamide in combination with docetaxel and ADT compared to the control arm.

Impairment due to pain

For the endpoint of impairment due to pain, assessed using items 9a-g of the BPI-SF, there was a statistically significant difference to the advantage of darolutamide in combination with docetaxel and ADT based on the mean differences. However, the 95% confidence interval of the standardised mean difference is not completely outside the irrelevance range of -0.2 to 0.2. Thus, it cannot be inferred that the observed effect is relevant.

Pain intensity

Furthermore, evaluations of the BPI-SF for items 3-6 are available for pain intensity. The results for the endpoint are not used for the present assessment; otherwise, the results of item 3 would be considered twice. Therefore, they are only presented additionally.

Symptomatology (NFPSI-17)

For the endpoint categories of morbidity and health-related quality of life, the pharmaceutical company submits evaluations of the NFPSI-17. The NFPSI-17 is a tool of the Functional Assessment of Chronic Illness [FACIT] questionnaire system and was derived from the Functional Assessment of Cancer Therapy - Prostate (FACT-P). The NFPSI-17 was developed to assess symptomatology in patients with advanced prostate cancer and consists of a total of 17 items. The first 10 items cover symptoms of the disease and are combined to form the DRS-P subscale. Item 11 cover the emotional burden of the symptomatology and forms its own subscale (Disease-Related Symptoms - Emotional [DRS-E]). Items 12 to 15 cover side effects of the treatment and form a separate subscale (TSE). Items 16 and 17 cover the general quality of life and form the subscale FWB (Function and Well-Being). Subscores can be created for each of the four subscales. In addition, according to the scoring guidelines, a total score can be created for all 17 items (NFPSI-17 Total). The subscales DRS-P and TSE can be clearly assigned to the symptomatology. The other 3 items of the subscales DRS-E and FWB are considered unsuitable to completely represent the complex construct of health-related quality of life. They also cannot be specifically assigned to the symptomatology. Therefore, only the subscales DRS-P and TOS are used to derive the additional benefit for the present benefit assessment and assigned to the endpoint category of morbidity.

The pharmaceutical company submits analyses on mean differences for the subscale TOS. There is a statistically significant difference to the advantage of darolutamide in combination with docetaxel and ADT. However, the 95% confidence interval of the standardised mean

difference is not completely outside the irrelevance range of -0.2 to 0.2. Thus, it cannot be inferred that the observed effect is relevant.

For the DRS-P subscale, the pharmaceutical company submits pre-specified responder analyses for the first-time deterioration by ≥ 3 points (scale range 0 to 40). This procedure does not correspond to the specifications of the module template with regard to response criteria for complex scales. With its written statement, the pharmaceutical company submits correspondingly corrected analyses used for the assessment. There is no statistically significant difference between the treatment arms here.

Overall, there is an additional benefit of darolutamide in combination with docetaxel and ADT in the endpoint category of morbidity, resulting from the advantages in the endpoints of symptomatic skeletal events and worst pain.

Quality of life

In line with the above comments on NFPSI-17, the ARASENS study does not provide data on health-related quality of life.

Side effects

Adverse events (AEs) in total

Nearly all patients in the ARASENS 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, in the area of specific adverse events, there are statistically significant differences to the disadvantage of darolutamide in combination with docetaxel and ADT with respect to the endpoints of skin and subcutaneous tissue disorders (SOC, severe AE) and hypertension (PT, severe AE); however, there is a statistically significant advantage for the endpoint of bone pain (PT, 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 darolutamide in combination with docetaxel and ADT, results from the ARASENS study are available for the endpoint categories of mortality, morbidity and side effects.

For the endpoint of overall survival, there is a clear advantage of darolutamide in combination with docetaxel and ADT over docetaxel in combination with ADT.

In the morbidity endpoint category, advantages are shown for darolutamide in combination with docetaxel and ADT for the endpoints of symptomatic skeletal events and worst pain. With regard to patient-reported symptomatology, measured using the NFPSI-17 tool, there were no assessment relevant differences between the treatment arms.

With regard to health-related quality of life, no data were collected in the ARASENS study.

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, the specific adverse events alone show disadvantages for the endpoints of skin and subcutaneous tissue disorders (SOC, AE) and hypertension (PT, severe AE) as well as an advantage for the endpoint of bone pain (PT, severe AE).

In the overall analysis, the positive effects in the endpoint categories of mortality and morbidity are therefore not offset by any disadvantages.

As a result, the G-BA found a considerable additional benefit of darolutamide in combination with docetaxel and ADT for the treatment of adult males with metastatic hormone-sensitive prostate cancer compared to docetaxel in combination with ADT.

Reliability of data (probability of additional benefit)

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

The endpoint-specific risk of bias for the endpoint of overall survival is also rated as low.

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

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the medicinal product Nubeqa with the active ingredient darolutamide.

The therapeutic indication assessed here is as follows:

"Nubeqa is indicated for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel and androgen deprivation therapy."

The appropriate comparator therapy was determined to be:

- conventional androgen deprivation in combination with apalutamide

or

- conventional androgen deprivation in combination with enzalutamide

or

- conventional androgen deprivation in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed, high-risk prostate cancer)

or

- conventional androgen deprivation in combination with docetaxel with or without prednisone or prednisolone

.

For the benefit assessment, the pharmaceutical company submitted data from the randomised, double-blind, placebo-controlled, phase III ARASENS study, which compared darolutamide in combination with docetaxel and ADT versus docetaxel in combination with ADT.

For the endpoint of overall survival, there is a clear advantage of darolutamide in combination with docetaxel and ADT over docetaxel in combination with ADT.

In the morbidity category, advantages are shown for darolutamide in combination with docetaxel and ADT for the endpoints of symptomatic skeletal events and worst pain.

With regard to health-related quality of life, no data were collected in the ARASENS study.

There were no differences relevant to the assessment of the side effects.

In the overall assessment, the G-BA found a considerable additional benefit of darolutamide in combination with docetaxel and ADT over docetaxel in combination with ADT.

In particular, due to the low risk of bias at study level and for the endpoint of overall survival, the reliability of data for the additional benefit identified is classified in the "indication" category.

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

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

The G-BA bases its resolution on the patient numbers from the dossier submitted by the pharmaceutical company. These are based on the resolutions on apalutamide of 20.08.2020 and enzalutamide of 19.11.2021 in the therapeutic indication in question and are subject to uncertainties. Overall, it is assumed that the reported number of patients is an underestimate, since, on the one hand, patients from previous years with an mHSPC who have not developed resistance to ADT and are eligible for therapy with darolutamide are not taken into account. On the other, due to the too short observation period in the derivation (6 weeks after the start of ADT), patients who only develop metastasis after this period following ADT are neglected.

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 Nubeqa (active ingredient: darolutamide) at the following publicly accessible link (last access: 9 August 2023):

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

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

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

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: 1 September 2023).

Orchiectomy

The costs of an orchiectomy are calculated on the basis of the case flat fee revenues, which result from the valuation ratios of the respective DRG multiplied by the federal base rate value of 2023 (€ 4,000.71). Furthermore, the nursing revenue is included in the inpatient costs. This is calculated from the average length of stay of the concerned DRG multiplied by the nursing fee Section 15 para. 2a KHEntgG (Act on Fees for Full and Semi-inpatient Hospital Services) (€ 230) and the treatment-specific nursing fee valuation ratio.

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.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Darolutamide in combination with docetaxel and androgen deprivation therapy				
Darolutamide	Continuously, 2 x daily	365	1	365.0
Docetaxel	1 x every 21 days	6	1	6.0
if applicable, prednisone	2 x daily	6	21	126.0
if applicable, prednisolone	2 x daily	6	21	126.0
Androgen deprivation				
Buserelin	Continuously, every 3 months	4	1	4.0
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
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
Relugolix	Continuously, 1 x daily	365	1	365.0
Orchiectomy	once		3.6 (average length of stay)[2]	-
Appropriate comparator therapy				
Conventional androgen deprivation in combination with apalutamide				
Androgen deprivation				
Buserelin	Continuously, every 3 months	4	1	4.0
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
Degarelix	Continuously, 1 x monthly	12	1	12.0
Relugolix	Continuously, 1 x daily	365	1	365.0
Orchiectomy	once		3.6 (average length of stay)[2]	-
Apalutamide	Continuously, 1 x daily	365	1	365.0
Conventional androgen deprivation in combination with enzalutamide				
Androgen deprivation				
Buserelin	Continuously, every 3 months	4	1	4.0
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

[2] Case Flat Fee Catalogue and Nursing Revenue Catalogue 2023, https://www.g-drg.de/ag-drg-system-2023/fallpauschalen-katalog/fallpauschalen-katalog-20232, accessed on 04.07.2023

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Degarelix	Continuously, 1 x monthly	12	1	12.0
Relugolix	Continuously, 1 x daily	365	1	365.0
Orchiectomy	once		3.6 (average length of stay)[2]	-
Enzalutamide	Continuously, 1 x daily	365	1	365.0
Conventional androgen deprivation in combination with abiraterone acetate and prednisone or prednisolone				
Androgen deprivation				
Buserelin	Continuously, every 3 months	4	1	4.0
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
Degarelix	Continuously, 1 x monthly	12	1	12.0
Relugolix	Continuously, 1 x daily	365	1	365.0
Orchiectomy	once		3.6 (average length of stay)[2]	-
Abiraterone acetate	Continuously, 1 x daily	365	1	365.0
Prednisone	Continuously, 1 x daily	365	1	365.0
Prednisolone	Continuously, 1 x daily	365	1	365.0
Conventional androgen deprivation in combination with docetaxel with or without prednisone or prednisolone				
Androgen deprivation				
Buserelin	Continuously, every 3 months	4	1	4.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
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
Degarelix	Continuously, 1 x monthly	12	1	12.0
Relugolix	Continuously, 1 x daily	365	1	365.0
Orchiectomy	once		3.6 (average length of stay)[2]	-
Docetaxel	1 x every 21 days	6	1	6.0
if applicable, prednisone	2 x daily	6	21	126.0
if applicable, prednisolone	2 x daily	6	21	126.0

Consumption:

The average body measurements of adult males were applied for dosages depending on body weight or body surface area (average body height: 1.79 m; average body weight: 85 kg). This results in a body surface area of 2.04 m² (calculated according to Du Bois 1916).[3]

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					
Darolutamide in combination with docetaxel and androgen deprivation therapy					
Darolutamide	600 mg	1200 mg	4 x 300 mg	365.0	1460 x 300 mg

[3] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/.

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Docetaxel	75 mg/m² = 153 mg	153 mg	1 x 160 mg	6.0	6.0 x 160 mg
if applicable, prednisone	5 mg	10 mg	2 x 5 mg	126.0	252.0 x 5 mg
if applicable, prednisolone	5 mg	10 mg	2 x 5 mg	126.0	252.0 x 5 mg
Androgen deprivation					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4.0 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4.0 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4.0 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2.0 x 22.5 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12.0 x 80 mg
Relugolix	120 mg	120 mg	1 x 120 mg	365.0	365.0 x 120 mg
Orchiectomy	One-off intervention				
Appropriate comparator therapy					
Conventional androgen deprivation in combination with apalutamide					
Androgen deprivation					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4.0 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4.0 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4.0 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2.0 x 22.5 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12.0 x 80 mg
Relugolix	120 mg	120 mg	1 x 120 mg	365.0	365.0 x 120 mg
Orchiectomy	One-off intervention				
Apalutamide	240 mg	240 mg	4 x 60 mg	365.0	1,460.0 x 60 mg
Conventional androgen deprivation in combination with enzalutamide					
Androgen deprivation					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4.0 x 9.45 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
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4.0 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4.0 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2.0 x 22.5 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12.0 x 80 mg
Relugolix	120 mg	120 mg	1 x 120 mg	365.0	365.0 x 120 mg
Orchiectomy	One-off intervention				
Enzalutamide	160 mg	160 mg	4 x 40 mg	365	1,460.0 x 40 mg
Conventional androgen deprivation in combination with abiraterone acetate and prednisone or prednisolone					
Androgen deprivation					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4.0 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4.0 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4.0 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2.0 x 22.5 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12.0 x 80 mg
Relugolix	120 mg	120 mg	1 x 120 mg	365.0	365.0 x 120 mg
Orchiectomy	One-off intervention				
Abiraterone acetate	1,000 mg	1,000 mg	4 x 250 mg	365.0	1460.0 x 250 mg
Prednisone	5 mg	5 mg	1 x 5 mg	365.0	365.0 x 5 mg
Prednisolone	5 mg	5 mg	1 x 5 mg	365.0	365.0 x 5 mg
Conventional androgen deprivation in combination with docetaxel with or without prednisone or prednisolone					
Androgen deprivation					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4.0 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4.0 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4.0 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2.0 x 22.5 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12.0 x 80 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
Relugolix	120 mg	120 mg	1 x 120 mg	365.0	365.0 x 120 mg
Orchiectomy	One-off intervention				
Docetaxel	75 mg/m² = 153 mg	153 mg	1 x 160 mg	6.0	6.0 x 160 mg
if applicable, prednisone	5 mg	10 mg	2 x 5 mg	126.0	252.0 x 5 mg
if applicable, prednisolone	5 mg	10 mg	2 x 5 mg	126.0	252.0 x 5 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with 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.

Orchiectomy

Calculation year	DRG	Average length of stay [d]	DRG valuation ratio (main department)	Federal base case value	Nursing revenue valuation ratio	Nursing fee	Case flat fee revenue	Nursing revenue	Total case flat fee revenue and nursing revenue
Orchiectomy									
2023	M04B	3.6	0.884	€ 4,000.71	0.7902	€ 230	€ 3,536.63	€ 654.29	€ 4190.92

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					
Darolutamide in combination with docetaxel and androgen deprivation therapy					
Darolutamide 300 mg	112 FCT	€ 3,840.84	€ 2.00	€ 370.39	€ 3,468.45
Docetaxel 160 mg	1 CIS	€ 515.78	€ 2.00	€ 23.94	€ 489.84
Prednisolone 5 mg[4]	100 TAB	€ 15.43	€ 2.00	€ 0.33	€ 13.10
Prednisone 5 mg[4]	100 TAB	€ 16.74	€ 2.00	€ 0.43	€ 14.31
Buserelin	2 PS	€ 1,114.57	€ 2.00	€ 104.71	€ 1,007.86
Goserelin	2 IMP	€ 1,174.45	€ 2.00	€ 110.40	€ 1,062.05
Leuprorelin	2 IMP	€ 730.78	€ 2.00	€ 86.93	€ 641.85
Triptorelin	1 DSS	€ 1,075.11	€ 2.00	€ 100.97	€ 972.14
Degarelix 80 mg	3 PLI	€ 591.88	€ 2.00	€ 55.10	€ 534.78
Relugolix 120 mg	90 FCT	€ 671.17	€ 2.00	€ 62.63	€ 606.54
Appropriate comparator therapy					
Docetaxel 160 mg	1 CIS	€ 515.78	€ 2.00	€ 23.94	€ 489.84
Prednisolone 5 mg[4]	100 TAB	€ 15.43	€ 2.00	€ 0.33	€ 13.10
Prednisone 5 mg[4]	100 TAB	€ 16.74	€ 2.00	€ 0.43	€ 14.31
Buserelin	2 FER	€ 1,114.57	€ 2.00	€ 104.71	€ 1,007.86
Goserelin	2 IMP	€ 1,174.45	€ 2.00	€ 110.40	€ 1,062.05
Leuprorelin	2 IMP	€ 730.78	€ 2.00	€ 86.93	€ 641.85
Triptorelin	1 DSS	€ 1,075.11	€ 2.00	€ 100.97	€ 972.14
Degarelix 80 mg	3 PLI	€ 591.88	€ 2.00	€ 55.10	€ 534.78
Relugolix 120 mg	90 FCT	€ 671.17	€ 2.00	€ 62.63	€ 606.54
Apalutamide	112 FCT	€ 2,831.43	€ 2.00	€ 113.15	€ 2,716.28
Enzalutamide	112 FCT	€ 3,193.33	€ 2.00	€ 127.91	€ 3,063.42
Abiraterone acetate	120 TAB	€ 137.75	€ 2.00	€ 16.00	€ 119.75
Abbreviations: PS = prefilled syringes; FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; IMP = implant; PSI = powder and solvent for solution for injection; TAB = tablets; DSS = dry substance with solvent					

[4] Fixed reimbursement rate

Costs for additionally required SHI services:

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

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

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

Other SHI services:

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

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

2.5 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.

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

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 28 June 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 24 March 2023 the pharmaceutical company submitted a dossier for the benefit assessment of darolutamide to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 27 March 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 darolutamide.

The dossier assessment by the IQWiG was submitted to the G-BA on 26 June 2023, and the written statement procedure was initiated with publication on the G-BA website on 3 July 2023. The deadline for submitting statements was 24 July 2023.

The oral hearing was held on 7 August 2023.

By letter dated 8 August 2023, 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 25 August 2023.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 12 September 2023, and the proposed resolution was approved.

At its session on 21 September 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	28 June 2022	Determination of the appropriate comparator therapy
Working group Section 35a	3 August 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 August 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	16 August 2023 6 September 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	12 September 2023	Concluding discussion of the draft resolution
Plenum	21 September 2023	Adoption of the resolution on the amendment of the AM-RL

Berlin, 21 September 2023

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

Prof. Hecken