Gemeinsamer Bundesausschuss

Justification

to 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 and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V Darolutamide (new therapeutic indication: metastatic hormone-sensitive prostate cancer, in combination with androgen deprivation therapy)

of 19 February 2026

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies the pharmaceutical company have 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 decide on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient 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 17 July 2025, 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 from 12.12.2008, sentence 7).

On 12 August 2025, i.e. at the latest within four weeks of informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with

Chapter 5 Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient darolutamide with the new therapeutic indication:

"Treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy"

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 17 November 2025 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 darolutamide compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA have 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 have made 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 androgen deprivation therapy.

Therapeutic indication of the resolution (resolution of 19 February 2026):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

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

- Conventional androgen deprivation in combination with apalutamide

  or

- conventional androgen deprivation in combination with enzalutamide

  or

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

- 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 darolutamide and docetaxel

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

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

- 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
- Darolutamide (combination with docetaxel and ADT): resolution of 21.09.2023

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 indication according to Section 35a paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy"). In this regard, there is a joint written statement from the German Society for Haematology and Medical Oncology (DGHO) and the German Society for Urology (DGU).

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 the context of the present therapeutic indication, conventional ADT refers to surgical or medicinal castration by therapy with GnRH agonists or GnRH antagonists. The disease of metastatic, hormone-sensitive prostate cancer constitutes a palliative treatment setting. Therefore, maintaining quality of life and symptom control are of particular importance.

The present guidelines unanimously recommend therapy with abiraterone acetate in combination with prednisone or prednisolone, apalutamide, enzalutamide or darolutamide in combination with docetaxel in addition to ADT. The rationale behind these recommendations is that relevant advantages in the therapeutic benefit could be shown for abiraterone acetate in combination with prednisone or prednisolone, apalutamide and enzalutamide compared with ADT alone as well as for darolutamide in combination with docetaxel and ADT compared with docetaxel and ADT. The guidelines also include recommendations for combination therapy (in addition to ADT) consisting of abiraterone acetate in combination with prednisone or prednisolone and docetaxel. However, this combination is not approved and therefore not considered as an appropriate comparator therapy.

In their written statement, the scientific-medical societies follow the recommendations of the guidelines on the individual active ingredients or combinations of active ingredients, but classify patients according to their suitability for chemotherapy and recommend abiraterone acetate in combination with prednisone or prednisolone, apalutamide and enzalutamide (each in addition to ADT) only for patients who are ineligible for chemotherapy. However, the scientific-medical societies' classification of patients covered by the present therapeutic indication into patients, who are suitable for chemotherapy and patients who are ineligible for chemotherapy, is not reflected so clearly in the guideline recommendations.

In the benefit assessment of 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 thereof was identified in the indirect comparison 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 in the indirect comparison 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). By resolution of 21.09.2023, an indication of a considerable additional benefit of darolutamide in combination with docetaxel and ADT compared with ADT in combination with docetaxel with or without prednisone or prednisolone could be found.

In the overall analysis, the treatment options of apalutamide, enzalutamide and darolutamide in combination with docetaxel - all treatment options, each in combination with ADT - 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 ADT represent another equally suitable comparator therapy in accordance with the marketing authorisation.

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

Any change to the appropriate comparator therapy requires a decision by the G-BA based on a prior review of the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of darolutamide in combination with androgen deprivation therapy is assessed as follows:

An additional benefit is not proven.

Justification:

In the absence of direct comparator studies of darolutamide in combination with ADT versus the appropriate comparator therapy, the pharmaceutical company presented an adjusted indirect comparison according to the procedure of Bucher et al. for the proof of an additional benefit. For the indirect comparison via the bridge comparator ADT (+ placebo), the pharmaceutical company included the ARANOTE study comparing darolutamide in combination with ADT versus ADT and the TITAN study comparing apalutamide in combination with ADT versus ADT.

Both studies are randomised, double-blind, controlled, multicentre phase III studies.

ARANOTE study

Adult men with mHSPC and an ECOG-PS ≤ 2 were enrolled in the study. Patients with exclusively regional lymph node metastases or known brain or leptomeningeal metastases were not enrolled. In addition, patients had to have started ADT using GnRH analogues (GnRH: gonadotropin-releasing hormone) or surgical castration within 12 weeks prior to randomisation. Prior treatment of prostate cancer with chemotherapy, including docetaxel, was not permitted.

A total of 669 patients were enrolled in the ARANOTE study and randomly assigned in a 2:1 ratio to treatment with darolutamide + ADT (N = 446) or placebo + ADT (N = 223). Randomisation was stratified by the presence or absence of visceral metastases, as well as previous or no previous local therapy.

Treatment with darolutamide was largely carried out in accordance with the product information. Patients in both study arms had to continue the ADT they had previously started during the study.

Treatment continued until radiological disease progression, withdrawal of consent, or unacceptable toxicity, although continued treatment beyond progression was possible.

Following the primary analysis of the endpoint of radiological progression-free survival (rPFS), an open-label phase was planned in the event of a positive risk-benefit assessment, in which patients in the control arm could switch to treatment with darolutamide + ADT.

The primary endpoint of the ARANOTE study is rPFS. Patient-relevant endpoints were assessed in the categories of mortality, morbidity, health-related quality of life and side effects.

TITAN study

Adult men with mHSPC and an ECOG-PS of 0 or 1, with metastases in the form of at least one confirmed bone lesion, were enrolled in the study. The patients enrolled had to have either undergone surgical castration or started medical ADT using GnRH analogues within a period

of 14 days to three months prior to randomisation. Pretreatment with up to 6 cycles of docetaxel was permitted.

The total of 1,052 patients enrolled in the study were randomised in a 1:1 ratio, stratified by Gleason score (< 7 vs ≥ 7), geographical region (North America and Europe vs all other countries) and pretreatment with docetaxel (yes vs no).

Treatment with apalutamide largely corresponded to the product information. Patients were treated until disease progression or unacceptable toxicity, after which they could switch to subsequent therapy.

In the event of a positive study result, an open-label extension phase, in which patients in the control arm could switch to apalutamide + ADT, was planned.

Co-primary endpoints of the study were overall survival and rPFS. Other patient-relevant endpoints were assessed in the categories of mortality, morbidity, health-related quality of life and side effects.

On the adjusted indirect comparison according to Bucher

Overall, there were some differences between the ARANOTE and TITAN studies in terms of study and patient characteristics (e.g. with regard to the permission for pretreatment with docetaxel or the ECOG-PS of patients), but none of these differences fundamentally call into question the similarity for the execution of an adjusted indirect comparison via the bridge comparator placebo + ADT.

Two data cut-offs are available for each of the two studies. For the ARANOTE study, a first data cut-off from 07.06.2024 is available for the pre-specified primary analysis of the rPFS endpoint, and a second data cut-off from 10.01.2025 is available for the pre-specified final analysis of the overall survival endpoint. For the TITAN study, a first data cut-off from 23.11.2018 is available for the pre-specified interim analysis of the overall survival endpoint and final analysis of the rPFS endpoint, as well as a second data cut-off from 07.09.2020 for the pre-specified final analysis of the overall survival endpoint.

The pharmaceutical company presented the results of the first data cut-off in the dossier for the indirect comparison of the ARANOTE and TITAN studies respectively. For the ARANOTE study, they justify the choice of the data cut-off by stating that 27% of patients in the control arm had started treatment with darolutamide + ADT at the second data cut-off and that the data cut-off therefore showed a potentially high risk of bias. For the TITAN study, the pharmaceutical company did not mention in the dossier that a 2nd data cut-off was also performed.

The execution of an indirect comparison of the two ARANOTE and TITAN studies at the respective 1st data cut-off is considered suitable. In both studies, this data cut-off took place approximately 3 years after the start of the study, and in each case it was the last point in time before unblinding of the study and the possibility of switching treatment from placebo + ADT to the treatment of the intervention arm.

Extent and probability of the additional benefit

Mortality

For the endpoint of overall survival, the adjusted indirect comparison showed no statistically significant difference between darolutamide in combination with ADT and apalutamide in combination with ADT.

For overall survival, an additional benefit of darolutamide in combination with ADT is therefore not proven.

Morbidity

Symptomatic skeletal events

The composite endpoint of symptomatic skeletal events in the studies consists of the following subcomponents:

- Carrying out external beam radiation therapy to alleviate skeletal symptoms (ARANOTE) or carrying out bone irradiation (TITAN)
- New symptomatic pathological bone fractures (ARANOTE) or occurrence of new symptomatic pathological fracture (TITAN)
- Occurrence of spinal cord compression (ARANOTE and TITAN)
- Tumour-related orthopaedic surgical intervention (ARANOTE) or bone surgery (TITAN)

In principle, the endpoint of symptomatic skeletal events is relevant for the benefit assessment. However, information on the occurrence of the individual subcomponents is missing in the dossier for the TITAN study. This information would be necessary for the assessment of the results of this endpoint in order to be able to make statements about the direction of effect of the subcomponents, for instance. Consequently, no suitable data are available from the TITAN study for the benefit assessment, and the indirect comparison submitted by the pharmaceutical company for this endpoint is therefore not used.

Fatigue (BFI) and health status (EQ-5D VAS)

In the ARANOTE study, no data on fatigue and health status were collected using the BFI or EQ-5D VAS. An adjusted indirect comparison is therefore not possible.

Worst pain (BPI-SF item 3)

For the endpoint of worst pain, the pharmaceutical company presented responder analyses of the time to confirmed deterioration and the time to confirmed improvement, each by at least 2 points, for the indirect comparison. According to the pharmaceutical company, no results were available for the operationalisation of first deterioration.

The responder analyses presented are not suitable for the benefit assessment in the present situation. In the ARANOTE and TITAN studies, the median observation periods in the intervention and control arms are initially adequately comparable. However, a continuous decline in the percentage of completed questionnaires, which differed between the study arms and cannot be explained solely by the patients, who died during the observation period, was observed over the course of the ARANOTE study. Therefore, it cannot be safely assumed that the observation periods are sufficiently equal over the course of the study. A difference in observation period between the treatment arms is particularly relevant if this results in a different number of surveys for the respective endpoint. In such a situation, responder analyses of the time to first deterioration are considered appropriate. The present analysis of the time to confirmed deterioration cannot be interpreted meaningfully.

However, there would not be adequate reliability of data even for this operationalisation to carry out an adjusted indirect comparison due to the declining return rate to the questionnaire over the course of the ARANOTE study and the differences in return rates between the study arms.

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

For the indirect comparison, the pharmaceutical company presented responder analyses of the time to first deterioration and the time to first improvement. For the endpoint of impairment due to pain, there is no adequate reliability of data to carry out an adjusted indirect comparison due to the declining return rate to the questionnaire over the course of the ARANOTE study and the differences in return rates between the study arms.

Overall, there is therefore no suitable data available in the morbidity endpoint category for an indirect comparison of the ARANOTE and TITAN studies, or the endpoints in the ARANOTE study show a high risk of bias, which means that the reliability of data required to carry out an adjusted indirect comparison is not given.

Quality of life

FACT-P

For the FACT-P, the pharmaceutical company presented responder analyses of the time to first deterioration and the time to first improvement, each by 10 points, for the indirect comparison.

Responder analyses with a response threshold of at least 15% of the scale range of the survey tool used must be presented for the benefit assessment. The 15% response threshold of the total FACT-P score is 23.4 points. The dossier contains results of the time to deterioration by 23.4 points only for the ARANOTE study and not for the TITAN study. The indirect comparison of the time to deterioration by 10 points, presented by the pharmaceutical company instead, does not meet the requirements and is therefore not used for the benefit assessment.

Side effects

Adverse events (AEs) in total

Adverse events occurred in nearly all patients in the ARANOTE and TITAN studies. The results are only presented additionally.

Serious adverse events (SAEs), severe AEs (CTCAE grade 3-4)

For the endpoints of SAEs and severe AEs (CTCAE grade ≥ 3), the adjusted indirect comparisons showed no statistically significant differences between darolutamide in combination with ADT and apalutamide in combination with ADT.

Therapy discontinuation due to AEs

Although there is a low risk of bias for the endpoint of therapy discontinuation due to adverse events in the ARANOTE and TITAN studies respectively, the reliability of data for the endpoints is still limited. Premature discontinuation of therapy for reasons other than AEs is a competing event for the endpoint of discontinuation due to AEs to be assessed. This means that, although AEs that would have led to therapy discontinuation may occur after discontinuation for other reasons, the "discontinuation" criterion can no longer be assessed for these AEs. It is not possible to estimate how many AEs this affects. Thus, there is inadequate reliability of data to carry out an adjusted indirect comparison.

In their statement, the pharmaceutical company presented an evaluation based on the Fine-Gray model for the endpoint of therapy discontinuation due to AEs for the ARANOTE study in order to assess the influence of competing events on the endpoint of therapy discontinuation due to AEs. However, no corresponding analysis and therefore no correspondingly adjusted indirect comparison is available for the TITAN study.

Regardless of this, the Fine-Gray model is a possible method for dealing with the competing event of death in the endpoints without fatal consequences. For the endpoint of therapy discontinuation due to AEs, there is however a methodological peculiarity in that the events of interest (relevant side effects leading to therapy discontinuation) may still occur after therapy discontinuation for other reasons, such as clinical progression of the disease, but are no longer collected. These uncertainties due to incomplete observations cannot be eliminated by a sensitivity analysis using the Fine-Gray model.

Specific AEs

In detail, the indirect comparison did not show any statistically significant difference for the specific AE of fall (PT).

Overall assessment

Based on an adjusted indirect comparison using the procedure of Bucher et al., results for overall survival and side effects are available for the assessment of the additional benefit of darolutamide in combination with androgen deprivation therapy (ADT), compared to the appropriate comparator therapy of apalutamide in combination with ADT, for the treatment of metastatic hormone-sensitive prostate cancer.

For the comparison via the bridge comparator of ADT (+ placebo), the pharmaceutical company included the ARANOTE study comparing darolutamide in combination with ADT versus ADT and the TITAN study comparing apalutamide in combination with ADT versus ADT.

For the endpoint of overall survival, the adjusted indirect comparison did not show any statistically significant difference. With regard to overall survival, an additional benefit of darolutamide in combination with ADT is therefore not proven.

For the patient-reported endpoints of symptomatology, health status and health-related quality of life, no usable data are available for an adjusted indirect comparison, or the requirements for the reliability of data for carrying out an indirect comparison are not met.

For the endpoints of serious adverse events (SAEs) and severe adverse events (CTCAE grade≥ 3) in side effects, the adjusted indirect comparison did not show any statistically significant differences. For the endpoint of therapy discontinuation due to AEs, there was inadequate reliability of data to carry out an adjusted indirect comparison.

In detail, for the specific AE of fall (PT), the indirect comparison likewise did not show any statistically significant difference.

The overall assessment therefore showed neither positive nor negative effects of darolutamide in combination with ADT compared to apalutamide in combination with ADT. An additional benefit of darolutamide in combination with ADT is therefore not proven.

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 androgen deprivation therapy."

The appropriate comparator therapy was determined to be:

- Conventional androgen deprivation therapy (ADT) in combination with apalutamide

or

- ADT in combination with enzalutamide

  or

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

  or

- ADT in combination with darolutamide and docetaxel.

The pharmaceutical company presented an adjusted indirect comparison of darolutamide in combination with androgen deprivation therapy (ADT) (ARANOTE study) versus apalutamide in combination with ADT (TITAN study) via the bridge comparator of ADT (+ placebo).

For the endpoint of overall survival, the adjusted indirect comparison did not show any statistically significant difference between the treatment groups.

For the patient-reported endpoints of symptomatology, health status and health-related quality of life, no usable data are available for an adjusted indirect comparison, or the requirements for the reliability of data for carrying out an indirect comparison are not met.

For the endpoints of serious adverse events (SAEs) and severe adverse events (CTCAE grade≥ 3) in side effects, the adjusted indirect comparison did not show any statistically significant differences. For the endpoint of therapy discontinuation due to AEs, there was inadequate reliability of data to carry out an adjusted indirect comparison.

The overall assessment therefore showed neither positive nor negative effects of darolutamide in combination with ADT compared to apalutamide in combination with ADT. An additional benefit of darolutamide in combination with ADT is therefore not proven.

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

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

The G-BA base their resolution on the patient numbers from the dossier submitted by the pharmaceutical company. These are based on the resolutions on apalutamide from 20.08.2020, enzalutamide from 19.11.2021 and darolutamide in combination with docetaxel and ADT from 21.09.2023 in the therapeutic indication in question and are subject to uncertainty. Overall, it is assumed that the number of patients is an underestimate, since, on the one hand, patients from previous years with mHSPC, who have not developed resistance to ADT and are eligible for therapy with darolutamide, are not taken into account in the figures. On the other, due to the too short observation period (6 weeks after the start of ADT), patients who only develop metastasis after this period following ADT are neglected in the figures.

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: 22 January 2026):

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 who are experienced in the treatment of patients with prostate cancer, and other doctors from other specialist groups participating in the Oncology Agreement.

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 December 2025). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

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 2025 (€ 4,394.22). 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) (€ 250) 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 is different 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 ADT				
Darolutamide	Continuously, 2 x daily	365	1	365
ADT				
Buserelin	Continuously, every 3 months	4	1	4
Goserelin	Continuously, every 3 months	4	1	4

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Leuprorelin	Continuously, every 3 months	4	1	4
Triptorelin	Continuously, every 6 months	2	1	2
Degarelix	Continuously, 1 x monthly	12	1	12
Relugolix:	Continuously, 1 x daily	365	1	365
Orchiectomy	once		3.8 (average length of stay)[2]	
Appropriate comparator therapy				
Conventional androgen deprivation in combination with apalutamide				
ADT				
Buserelin	Continuously, every 3 months	4	1	4
Goserelin	Continuously, every 3 months	4	1	4
Leuprorelin	Continuously, every 3 months	4	1	4
Triptorelin	Continuously, every 6 months	2	1	2
Degarelix	Continuously, 1 x monthly	12	1	12
Relugolix:	Continuously, 1 x daily	365	1	365
Orchiectomy	once		3.8 (average length of stay)	
Apalutamide	Continuously, 1 x daily	365	1	365
Conventional androgen deprivation in combination with enzalutamide				
ADT				
Buserelin	Continuously, every 3 months	4	1	4

[2] Case Flat Fee Catalogue and Nursing Revenue Catalogue 2025, https://www.g-drg.de/ag-drg-system-2025/fallpauschalen-katalog, accessed on 04.11.2025

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
Leuprorelin	Continuously, every 3 months	4	1	4
Triptorelin	Continuously, every 6 months	2	1	2
Degarelix	Continuously, 1 x monthly	12	1	12
Relugolix:	Continuously, 1 x daily	365	1	365
Orchiectomy	once		3.8 (average length of stay)	
Enzalutamide	Continuously, 1 x daily	365	1	365
Conventional androgen deprivation in combination with abiraterone acetate and prednisone or prednisolone				
ADT				
Buserelin	Continuously, every 3 months	4	1	4
Goserelin	Continuously, every 3 months	4	1	4
Leuprorelin	Continuously, every 3 months	4	1	4
Triptorelin	Continuously, every 6 months	2	1	2
Degarelix	Continuously, 1 x monthly	12	1	12
Relugolix:	Continuously, 1 x daily	365	1	365
Orchiectomy	once		3.8 (average length of stay)	
Abiraterone acetate	Continuously, 1 x daily	365	1	365
Prednisone	Continuously, 1 x daily	365	1	365
Prednisolone	Continuously, 1 x daily	365	1	365
Conventional androgen deprivation in combination with darolutamide and docetaxel				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
ADT				
Buserelin	Continuously, every 3 months	4	1	4
Goserelin	Continuously, every 3 months	4	1	4
Leuprorelin	Continuously, every 3 months	4	1	4
Triptorelin	Continuously, every 6 months	2	1	2
Degarelix	Continuously, 1 x monthly	12	1	12
Relugolix:	Continuously, 1 x daily	365	1	365
Orchiectomy	once		3.8 (average length of stay)	
Darolutamide	Continuously, 2 x daily	365	1	365
Docetaxel	1 x every 21 days	6	1	6
If applicable Prednisone	2 x daily	6	21	126
If applicable Prednisolone	2 x daily	6	21	126

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: 85.8 kg). This results in a body surface area of 2.05 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					

[3] Federal Statistical Office, Wiesbaden 2021: http://www.gbe-bund.de, accessed on 04.11.2025

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Darolutamide in combination with ADT					
Darolutamide	600 mg	1,200 mg	4 x 300 mg	365	1,460 x 300 mg
ADT					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4	4 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2	2 x 22.5 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12	12 x 80 mg
Relugolix:	120 mg	120 mg	1 x 120 mg	365	365 x 120 mg
Orchiectomy	One-off intervention				
Appropriate comparator therapy					
Conventional androgen deprivation in combination with apalutamide					
ADT					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4	4 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2	2 x 22.5 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12	12 x 80 mg
Relugolix:	120 mg	120 mg	1 x 120 mg	365	365 x 120 mg
Orchiectomy	One-off intervention				
Apalutamide	240 mg	240 mg	1 x 240 mg	365	365 x 240 mg
Conventional androgen deprivation in combination with enzalutamide					
ADT					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4	4 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2	2 x 22.5 mg

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Degarelix	80 mg	80 mg	1 x 80 mg	12	12 x 80 mg
Relugolix:	120 mg	120 mg	1 x 120 mg	365	365 x 120 mg
Orchiectomy	One-off intervention				
Enzalutamide	160 mg	160 mg	4 x 40 mg	365	1,460 x 40 mg
Conventional androgen deprivation in combination with abiraterone acetate and prednisone or prednisolone					
ADT					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4	4 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2	2 x 22.5 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12	12 x 80 mg
Relugolix:	120 mg	120 mg	1 x 120 mg	365	365 x 120 mg
Orchiectomy	One-off intervention				
Abiraterone acetate	1,000 mg	1,000 mg	1 x 1,000 mg	365	365 x 1,000 mg
Prednisone	5 mg	5 mg	1 x 5 mg	365	365 x 5 mg
Prednisolone	5 mg	5 mg	1 x 5 mg	365	365 x 5 mg
Conventional androgen deprivation in combination with darolutamide and docetaxel					
ADT					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4	4 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2	2 x 22.5 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12	12 x 80 mg
Relugolix:	120 mg	120 mg	1 x 120 mg	365	365 x 120 mg
Orchiectomy	One-off intervention				

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Darolutamide	600 mg	1,200 mg	4 x 300 mg	365	1,460 x 300 mg
Docetaxel	75 mg/m² = 153.8 mg	153.8 mg	1 x 160 mg	6	6 x 160 mg
If applicable Prednisone	5 mg	10 mg	2 x 5 mg	126	252 x 5 mg
If applicable Prednisolone	5 mg	10 mg	2 x 5 mg	126	252 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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

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									
2025	M04 B	3.8	0.872	€ 4,394.22	0.7914	€ 250	€ 3,831.76	€ 751.83	€ 4,583.59

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 ADT					

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
Darolutamide 300 mg	112 FCT	€ 3,526.39	€ 1.77	€ 0.00	€ 3,524.62
Buserelin 9.45 mg	2 PS	€ 1,265.91	€ 1.77	€ 69.46	€ 1,194.68
Goserelin 10.8 mg	2 IMP	€ 1,266.34	€ 1.77	€ 69.49	€ 1,195.08
Leuprorelin 11.25 mg	2 IMP	€ 730.78	€ 1.77	€ 86.93	€ 642.08
Triptorelin 22.5 mg	1 DSS	€ 1,162.65	€ 1.77	€ 63.74	€ 1,097.14
Degarelix 80 mg	3 PSI	€ 591.88	€ 1.77	€ 32.14	€ 557.97
Relugolix 120 mg	90 FCT	€ 563.92	€ 1.77	€ 30.59	€ 531.56
Appropriate comparator therapy					
Buserelin 9.45 mg	2 PS	€ 1,265.91	€ 1.77	€ 69.46	€ 1,194.68
Goserelin 10.8 mg	2 IMP	€ 1,266.34	€ 1.77	€ 69.49	€ 1,195.08
Leuprorelin 11.25 mg	2 IMP	€ 730.78	€ 1.77	€ 86.93	€ 642.08
Triptorelin 22.5 mg	1 DSS	€ 1,162.65	€ 1.77	€ 63.74	€ 1,097.14
Degarelix 80 mg	3 PSI	€ 591.88	€ 1.77	€ 32.14	€ 557.97
Relugolix 120 mg	90 FCT	€ 563.92	€ 1.77	€ 30.59	€ 531.56
Darolutamide 300 mg	112 FCT	€ 3,526.39	€ 1.77	€ 0.00	€ 3,524.62
Apalutamide 240 mg	28 FCT	€ 2,680.90	€ 1.77	€ 0.00	€ 2,679.13
Docetaxel 160 mg	1 CIS	€ 515.78	€ 1.77	€ 23.94	€ 490.07
Enzalutamide 40 mg	112 FCT	€ 3,123.20	€ 1.77	€ 0.00	€ 3,121.43
Abiraterone acetate 1,000 mg	28 FCT	€ 152.99	€ 1.77	€ 11.21	€ 140.01
Prednisone 5 mg	100 TAB	€ 16.74	€ 1.77	€ 0.43	€ 14.54
Prednisolone 5 mg	100 TAB	€ 15.43	€ 1.77	€ 0.33	€ 13.33
Abbreviations: FCT = film-coated tablets; PS = prefilled syringes; CIS = concentrate for the preparation of an infusion solution; IMP = implant; DSS = dry substance with solvent; PSI = powder and solvent for solution for injection; TAB = tablets					

LAUER-TAXE® last revised: 15 December 2025

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 1 October 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 agents 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 are not added to the pharmacy sales price but rather follow the rules for calculating in the 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 designate 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 have 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 have 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 requirements 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 have 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:

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

The designated medicinal products concern in each case an active ingredient which may be used in combination therapy with the assessed medicinal product in the context of a therapeutic indication specified in the product information for the assessed medicinal product. According to the requirements in the product information, this therapeutic application concerns androgen deprivation therapy for the treatment of adult men with metastatic hormone-sensitive prostate cancer.
For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the requirements in the product information, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.
References:

- Product information for darolutamide (Nubeqa); NUBEQA® 300 mg film-coated tablets; last revised: July 2025
- Product information for relugolix (Orgovyx); Orgovyx 120 mg film-coated tablets; last revised: September 2025

Supplement to Annex XIIa of the Pharmaceuticals Directive

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive and provided with patient-group-related information on the period of validity of the designation.

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 their session on 8 October 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 12 August 2025, 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 13 August 2025 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 13 November 2025, and the written statement procedure was initiated with publication on the G-BA website on 17 November 2025. The deadline for submitting written statements was 8 December 2025.

The oral hearing was held on 12 January 2026.

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 subcommittee session on 10 February 2026, and the draft resolution was approved.

At their session on 19 February 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	8 October 2024	Determination of the appropriate comparator therapy
Working group Section 35a	17 December 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	12 January 2026	Conduct of the oral hearing
Working group Section 35a	21 January 2026 4 February 2026	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	10 February 2026	Concluding discussion of the draft resolution
Plenum	19 February 2026	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 19 February 2026

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

Prof. Hecken