# Justification

Gemeinsamer Bundesausschuss

## to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Enzalutamide (Reassessment after the Deadline: Non-metastatic Castration-resistant Prostate Cancer)

of 5 November 2020

**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 based on 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 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 forms part of the Pharmaceuticals Directive.

## 2. Key points of the resolution

On 19 November 2018, the pharmaceutical company first submitted a dossier for the early benefit assessment of the active ingredient enzalutamide (Xtandi) for the present therapeutic indication. The resolution of 16 May 2019 passed by the G-BA in this procedure was limited until 15 May 2020.

In accordance with Section 4, paragraph 3, No. 5 AM-NutzenV in conjunction with Chapter 5, Section 8, paragraph 1, No. 5 VerfO, the benefit assessment procedure for the medicinal product Xtandi shall start again on the day the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 5 VerfO on 14 May 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 17 August 2020, 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 enzalutamide compared with the appropriate comparator therapy could be determined based on the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements

submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit based on their therapeutic relevance (qualitative) according to 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 set aside in the benefit assessment of enzalutamide.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at 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 enzalutamide (Xtandi) in accordance with the product information

Xtandi is indicated for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC).

### 2.1.2 Appropriate comparator therapy

Adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC)

- A wait-and-see approach while maintaining the existing conventional androgen deprivation therapy (ADT).

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to 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 applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. Medicinal products with the following active ingredients are approved for the present therapeutic indication: apalutamide, bicalutamide, darolutamide, flutamide cyproterone

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

acetate, degarelix, buserelin, goserelin, leuprorelin, triptorelin, and estramustin (cytostatic agent).

On 2. In principle, radiotherapy and surgical treatment can be considered as non-medical therapies for non-metastatic prostate cancer. It is assumed that percutaneous radiotherapy is excluded as a possibility for patients who are undergoing therapy. This also applies to surgical therapy, which is why the non-medicinal treatments described above are not considered as appropriate comparator therapies.

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

- Apalutamide (Resolution of 1 October 2020)
- Darolutamide (Resolution of 15 October 2020).

The G-BA is assessing non-medicinal treatments such as interstitial brachytherapy for localised prostate cancer and proton therapy for prostate cancer as new methods for diagnosis and treatment. Both assessment procedures are currently on hold (Resolution of 17 December 2009/Resolution of 19 June 2008).

On 4. The generally accepted state of medical knowledge for the indication was established by means of a systematic search for guidelines and reviews of clinical studies.

Thus, the evidence for treatment options in the present therapy situation is very limited. No relevant Cochrane reviews or systematic reviews were identified. The data basis on the question of whether medicinal androgen deprivation should be continued unchanged, modified, or discontinued in the present therapy situation is both qualitatively weak and contradictory. However, the current guidelines predominantly recommend a wait-and-see approach with continuation of ADT.

With regard to secondary hormone manipulation, the active ingredients apalutamide and darolutamide were assessed in the present therapeutic indication within the scope of the benefit assessment according to Section 35a SGB V.

In the reassessment of apalutamide after the deadline, there was an indication of a minor additional benefit compared with a wait-and-see approach while maintaining the existing ADT (resolution of 1 October 2020).

Darolutamide has been available in the therapeutic indication being assessed since March 2020. In the benefit assessment on darolutamide, the resolution of 15 October 2020 found an indication of a considerable additional benefit. Darolutamide is thus a new treatment option, the therapeutic value of which cannot yet be conclusively assessed.

With regard to this recently completed benefit assessment procedure, no new definition of appropriate comparator therapy has been made in the present resolution for the purpose of defining the appropriate comparator therapy.

For the remaining antiandrogens, there is no proof of efficacy in clinically relevant endpoints. Chemotherapy is not recommended to treat non-metastatic castration-resistant prostate cancer.

Based on the evidence available, the G-BA considers the wait-and-see approach while maintaining the existing conventional androgen deprivation therapy to be the most appropriate comparator therapy in the treatment of adult men with non-metastatic castration-resistant prostate cancer.

Conventional androgen deprivation therapy in the present therapeutic indication implies surgical castration or pharmacological castration with GnRH agonists or GnRH antagonists.

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

### 2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of enzalutamide is assessed as follows:

Adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC)

Indication of a minor additional benefit.

Justification:

For the renewed benefit assessment after the expiry of the limited period of validity of the initial resolution of 16 May 2019, the pharmaceutical company presents results of the PROSPER study with a data cut-off of 15 October 2019. This third data cut-off of the study was conducted as a planned interim analysis for the overall survival endpoint after approximately 440 deaths.

The PROSPER study is a randomised, double-blind, placebo-controlled parallel group study. A total of 1401 patients with high-risk non-metastatic castration-resistant prostate cancer were included in the study and assigned to either the enzalutamide arm (intervention arm) or the placebo arm (comparator arm) at a ratio of 2:1. Patients in both arms also underwent or continued to undergo androgen deprivation therapy with a GnRH agonist or antagonist provided no orchiectomy had been performed. Based on the study regimes implemented in the PROSPER study, the placebo comparison is considered a sufficient approximation to the appropriate comparator therapy of a wait-and-see approach while maintaining the existing conventional ADT.

The mean age of the patients was 73 years, most of them were from Europe (49%), and they had received their diagnosis of prostate cancer a median of approximately 7 years prior to randomisation. Most patients (87%) had undergone androgen deprivation by pharmacological castration using GnRH agonists or GnRH antagonists, while only a small percentage (13%) had undergone orchiectomy for androgen deprivation.

The primary endpoint of the study was metastasis-free survival (MFS). Other endpoints included overall survival and endpoints in the categories morbidity (pain, health status), health-related quality of life, and adverse events.

Patients were treated until radiographic disease progression (defined as metastasis of bone and/or soft tissue), start of cytotoxic chemotherapy, use of androgen receptor inhibitors or other test substances, or therapy discontinuation at the discretion of the doctor or patient.

Once the therapy had been completed, there were no limitations regarding which type of follow-up treatment could be employed. The most frequent follow-up therapies administered in the study were docetaxel (intervention arm vs comparator arm: 20.2% vs 30.8%) and abiraterone acetate (intervention arm vs comparator arm: 16.3% vs 38.3%).

Follow-up was performed to ascertain overall survival until death and side effects within the first 30 days after treatment. Morbidity and quality of life endpoints were monitored in the first 30 days after therapy. For patients who had not yet progressed, morbidity and health-related quality of life data were collected beyond 30 days after therapy had concluded (every 16 weeks until death), provided they attended follow-up consultations.

The PROSPER study started in November 2013 and, according to information in Module 4 A, was completed on the a priori planned third data cut-off of 15 October 2019. Further a priori planned data cut-offs from the PROSPER study – 28 June 2017 (analysis on the MFS endpoint) and 31 May 2018 (interim analysis on the endpoint overall survival endpoint) – are available.

After the first data cut-off, the PROSPER study was unblinded on 8 September 2017. An unblinded enzalutamide extension phase (open-label period) was introduced by amendment to the study protocol on 26 January 2018. During this phase, patients of the comparator arm

were able receive enzalutamide at the doctor's discretion while retaining the existing ADT. In total, 87 patients (18.6%) of the comparator arm switched to enzalutamide treatment while maintaining the existing ADT (cross-over group) after the first data cut-off. In the enzalutamide extension phase, treatment with enzalutamide and ADT was continued until radiographic disease progression or beyond if the investigator thought there was a clinical benefit. Survival status, initiation of new treatments for prostate cancer, AEs, and concomitant medications were also surveyed. No further data on morbidity and quality of life were collected.

*On the implementation of conditions for a time limit*

The submission of the results of the planned interim analysis on overall survival after about 440 deaths (3rd data cut-off) for all endpoints used to demonstrate an additional benefit was requested as part of the limitation of the initial resolution. In the dossier, the pharmaceutical company derives the additional benefit for enzalutamide exclusively from the results of the 3rd data cut-off based on the endpoints on overall survival, time to start of a new antineoplastic therapy/cytotoxic chemotherapy, and adverse events. The other patient-relevant outcomes, especially the patient-reported endpoints on morbidity and health-related quality of life, were not presented in the dossier. According to the pharmaceutical company in the oral hearing, the patient-reported endpoints were no longer surveyed when the open label period came into force. For the present assessment, however, despite the lack of presentation in Module 4 A, the results of the 1st data cut-off of 28 June 2017 can be used for the endpoints surveyed by means of BPI-SF, EQ-5D VAS and FACT-P, which had formed the basis of the initial assessment. Because an event has already occurred in a large proportion of the study population for this data cut-off, it cannot be assumed that the results at a later evaluation date of the PROSPER study would deviate significantly from those of the first data cut-off. The same applies to the endpoint metastasis-free survival (MFS). For the endpoints overall survival and time to start of cytotoxic chemotherapy as well as the endpoints on adverse events, the results of the 3rd data cut-off from 15 October 2019 are presented.

Extent and probability of the additional benefit

Mortality

In the PROSPER study, overall survival was defined as the time from randomisation to death by any cause.

For the overall survival endpoint, there is a significant difference between treatment arms in favour of enzalutamide. The median survival time is 67.0 months in the intervention arm and 56.3 months in the comparator arm; this corresponds to a median prolongation of 10.7 months.

Although enzalutamide leads to an improvement in overall survival, the extent of the effect of enzalutamide compared with the wait-and-see approach, taking into account the remaining life expectancy of patients in the present therapy situation, is considered a relevant – but no more than a minor – improvement.

Morbidity

*Metastasis-free survival (MFS)*

The MFS endpoint in the PROSPER study was defined as the time from randomisation to initial evidence of radiographic progression according to RECIST1.1 criteria at any time, or death within 112 days after discontinuation of study medication without proof of radiographic progression. The MFS endpoint was assessed based on radiographic assessment of bone metastases and soft tissue metastases.

In the intervention arm, the MFS was significantly longer (median 21.9 months) than in the comparator arm.

In the operationalisation of the study, the MFS endpoint constitutes a combined endpoint combining mortality and morbidity endpoints. In the PROSPER study, the mortality endpoint component was calculated as an independent endpoint via the overall survival endpoint.

The morbidity component was not surveyed based on symptoms but rather exclusively by means of imaging procedures (radiologically determined disease progression according to the RECIST criteria) and thus solely based on primarily asymptomatic, not directly patient-relevant findings.

A direct assessment of the metastasis of the disease by means of a symptomatology perceived by the patients is not possible using the operationalisation chosen here. A differentiation between symptomatic and asymptomatic metastases is therefore also not possible. Against the background that metastasis is often asymptomatic in patients with castration-resistant prostate cancer, this point should be considered as highly relevant. In this regard, guidelines consistently differentiate between symptomatic and asymptomatic or slightly symptomatic prostate cancer patients, with distinct therapy recommendations in each case.

In addition, metastasis in patients receiving treatment for high-risk non-metastatic castration-resistant prostate cancer is not considered to be as prognostically relevant as it would be in other oncological indications, where metastasis potentially indicates treatment should be transitioned from curative to palliative care. The data available on the MFS endpoint indicate that enzalutamide delays but does not prevent metastasis.

As a result, there are considerable uncertainties in the significance of the results for this endpoint for patient-relevant benefit, which is why the endpoint MFS is not used in the present assessment.

*Time to start of cytotoxic chemotherapy*

The time to start of cytotoxic chemotherapy endpoint was defined in the PROSPER study as the time from randomisation to commencement of cytotoxic chemotherapy.

The current benefit assessment is based on a sensitivity analysis that takes into account the number of deaths. In the intervention arm, the time to the start of a cytotoxic chemotherapy was prolonged by 16.7 months. The difference is significant.

For patients with high-risk non-metastatic castration-resistant prostate cancer who so far at this stage of the disease have only been treated with conventional androgen deprivation, such a prolongation of time to initial treatment with cytotoxic chemotherapy, which is recognised to be associated with significant side effects, may be relevant.

Irrespective of the fundamental question whether the "time to start of a cytotoxic chemotherapy" endpoint should also be reflected in other relevant endpoints in order to be assessed as patient-relevant, in the present case, there are clear uncertainties as to the significance of the results. As a result, no conclusions on the additional benefit can be derived from the data available.

According to recommendations in the guidelines, any decision in the present therapeutic indication on the merits of switching from androgen deprivation to further therapeutic measures should be taken on a patient-individual basis. For this reason, the guidelines recommend patients with castration-resistant prostate cancer be differentiated into symptomatic and asymptomatic or slightly symptomatic cases, with distinct therapy recommendations. For this reason, it should not be assumed, particularly in the case of development of asymptomatic metastases or based on metastasis detection via imaging, that patients are generally treated with cytotoxic chemotherapy following androgen deprivation. In addition to cytotoxic chemotherapy, there are other established treatment options worth considering when treating metastasis. Information on how decisions were made whether to treat patients with

chemotherapy is essential for interpreting the results of the study. However, this was either not provided or not surveyed in the PROSPER study. The results for the endpoint time to start of cytotoxic chemotherapy are therefore not used in the present assessment.

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

Health status was assessed using the visual analogue scale of the EQ-5D questionnaire.

The IQWiG uses the mean change analysis in the dossier assessment. The difference between the study arms is not significant with respect to mean difference.

The study referred to as the basis for deriving Minimal Important Difference (MID) for responder analyses (Pickard *et al.*, 2007) was considered to by unsuitable by the IQWiG for substantiating the validity of the MID. This is justified because the work mentioned does not contain a longitudinal study to determine the MID; this is assumed in the current scientific discussion on deriving a valid MID. The IQWiG also does not consider the anchors ECOG-PS and FACT-G component scores used in the study to be suitable for deriving an MID.

In view of the fact that responder analyses based on MID have general advantages over an analysis of standardised mean differences in clinical evaluation of effects, and in view of the fact that the validation study in question has already been used in previous assessments, the G-BA will draw on the responder analyses in the present assessment to assess the effects on the symptomatology.

Analogous to the initial assessment, the data on the “time to first deterioration” by ≥ 7 points and ≥ 10 points are used. For both response criteria (≥ 7 points and ≥ 10 points), there are significant advantages for enzalutamide compared with the wait-and-see approach. In the intervention arm, the median time to deterioration of health status was prolonged by 3.6 months.

*Pain: Brief Pain Inventory Short Form (BPI-SF)*

In the PROSPER study, pain was assessed via the BPI-SF questionnaire as a patient-reported endpoint. There are no significant differences between the treatment groups for the endpoints worst pain (BPI-SF Item 3) and impairment due to pain (BPI-SF item 9a–g). The results for the endpoint "mean pain intensity" are not taken into account for the present assessment; had they been, the findings for item 3 would have been taken into account twice. They are presented additionally.

*Summary on morbidity*

In summary, only some of the available endpoints and study results would permit valid inferences to be made on morbidity. Based on this, a significant difference in favour of enzalutamide can be determined only for the endpoint health status using the EQ-5D VAS scale. However, in view of the long disease course of prostate cancer at this stage and the small difference established, this finding cannot be used to derive an additional benefit. In summary therefore, as a general finding no benefits or detriments can be identified for enzalutamide in the morbidity category.

Quality of life

*FACT-P*

In the PROSPER study, patients reported on their health-related quality of life via the FACT-P questionnaire.

There is no significant difference in the total score between the treatment arms. Only the total score was considered in the assessment of the additional benefit because this provides a

comprehensive overview of the data on patients' health-related quality of life. The individual sub-scales of the FACT-P are therefore presented additionally.

Side effects

*Total adverse events (AE)*

In the PROSPER study, approx. 94% of patients in the intervention arm and approx. 82% of patients in the comparator arm experienced an adverse event. The results for the endpoint total adverse events are presented additionally.

*Serious AE (SAE), severe AE (CTCAE grade ≥ 3), therapy discontinuations because of AE*

For the endpoints SAE, severe AE (CTCAE grade ≥ 3), and therapy discontinuations because of AE, there are no significant differences between the treatment arms.

*Specific AE*

For specific UE, an advantage in the endpoint "Renal and urinary disorders (SOC, severe AEs)" is offset by disadvantages in the endpoints "Psychiatric disorders (SOC, AEs)", "General disorders and administration site conditions (SOC, severe AEs)", "Nervous system disorders (SOC, severe AEs)", and "Hypertension (SMQ, severe AEs)".

In the overall assessment of the endpoint category side effects, neither an advantage nor a disadvantage can be identified for enzalutamide compared with the wait-and-see approach. In detail, differences can be seen only in the specific AE. There is one advantage and several disadvantages for enzalutamide compared with the wait-and-see approach.

Overall assessment

The renewed benefit assessment of enzalutamide for the treatment of adult males with high-risk non-metastatic castration-resistant prostate cancer (CRPC) draws on findings from the PROSPER study on overall survival, morbidity, health-related quality of life, and side effects.

The study compared enzalutamide with placebo. In both treatment arms, androgen deprivation therapy (ADT) was also carried out or continued in the absence of an orchiectomy. Based on the examination regimes carried out, the placebo comparison is regarded as a sufficient approximation to the appropriate comparator therapy of a wait-and-see approach while maintaining the existing conventional ADT.

The improvement achieved by enzalutamide in the endpoint category mortality compared with the wait-and-see approach is assessed as a relevant – but no more than minor – improvement taking into account the remaining life expectancy of patients in the current therapy situation.

In the morbidity endpoint, only some of the available endpoints or study results would permit valid inferences to be made. As a result, it was neither possible to establish benefits nor detriments of treatment with enzalutamide in general.

With regards to health-related quality of life, the effect of enzalutamide treatment was neither positive nor negative.

In terms of side effects, there is also no advantage or disadvantage of enzalutamide compared with a wait-and-see approach. In detail, significant differences can be seen only in the specific AE; there is one advantage and several disadvantages.

In the overall assessment of the results available on the patient-relevant endpoints, the advantage in overall survival is not offset by disadvantages in morbidity, health-related quality of life, and side effects.

As a result, for enzalutamide for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (nm-CRPC), the G-BA found a minor additional benefit

compared with the appropriate comparator therapy of a wait-and-see approach while maintaining the existing conventional 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 PROSPER study. The risk of bias at the study level is classified as low.

Because the benefit assessment is based on the results of only one study, at best indications of an additional benefit can be derived with regard to the reliability of data.

At the endpoint level, the risk of bias for overall survival is rated as low.

Against the background of the unblinding of the study or the change of treatment, the endpoint "therapy discontinuations because of adverse events" is also regarded as potentially highly biased.

All in all, the present data basis is subject to uncertainties. The uncertainties are not considered to be so high overall that a downgrading of the reliability of data would be justified for the overall assessment. In particular, the risk of bias of the endpoint overall survival is considered low. The reliability of data supporting the finding of an additional benefit must therefore be classified as "indication".

### 2.1.4 Summary of the assessment

The present assessment is a renewed benefit assessment of the active ingredient enzalutamide because of the expiry of the limitation of the resolution of 16 May 2019.

Enzalutamide is indicated for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer.

The G-BA determined that the wait-and-see approach, while maintaining the existing conventional androgen deprivation (ADT), was an appropriate comparator therapy.

In the randomised, double-blind PROSPER study, patients were randomised to either the enzalutamide or placebo arm. In both arms, androgen deprivation therapy was also maintained in the absence of an orchiectomy. The investigation regimes carried out in the PROSPER study are considered a sufficient approximation of the appropriate comparator therapy.

The improvement in overall survival achieved by enzalutamide compared with the wait-and-see approach is assessed as a relevant – but no more than minor – improvement, taking into account the remaining life expectancy of patients in the present therapy situation.

In the morbidity endpoint, only some of the available endpoints or study results would permit valid inferences to be made. As a result, it was neither possible to establish benefits nor detriments of treatment with enzalutamide in general.

With regards to health-related quality of life, the effect of enzalutamide treatment was neither positive nor negative.

In terms of side effects, there is also no advantage or disadvantage to enzalutamide compared with the wait-and-see approach. In detail, the specific adverse events alone reveal both one advantage and several disadvantages.

Overall, there is an indication of a minor additional benefit of apalutamide compared with a wait-and-see approach while maintaining existing conventional androgen deprivation.

## 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 derivation of the patient numbers carried out by the pharmaceutical company in the dossier is comprehensible. However, there are methodological weaknesses and uncertainties regarding the sources used. The pharmaceutical company initially bases the calculation on data on the 5-year prevalence. However, this does not sufficiently consider all patients with prostate cancer. With regard to the determination of the proportions of patients with castration-resistant prostate cancer, the lower limit is based on an abstract, which lacks detailed information on the characteristics and observation periods of the reported study population. The transferability of this proportion can therefore not be conclusively assessed. For the upper limit of this proportional value as well as for calculating the proportional value of patients with non-metastatic castration-resistant prostate cancer, the pharmaceutical company uses a publication based on data on patients who visited a medical practice. Because it is unclear to what extent the stage of the disease influences the frequency of visits to the doctor, further uncertainties arise.

In order to enable a consistent consideration of patient numbers in view of these uncertainties, taking into account the most recent resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the present therapeutic indication, this resolution is based on the relevant information from the resolutions on apalutamide of 1 October 2020 and darolutamide of 15 October 2020.

## 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 Xtandi (active ingredient: enzalutamide) at the following publicly accessible link (last access: 23 September 2020):

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

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

Patients who have not undergone surgical castration should continue receiving chemical castration with GnRH agonists or antagonists during treatment.

## 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 October 2020).

Treatment duration:

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 for each individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and 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 | | | | |
| Enzalutamide | continuously, 1 × daily | 365 | 1 | 365 |
| ADT | | | | |
| Degarelix | continuously, 1 × monthly | 12 | 1 | 12 |
| 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 |
| Appropriate comparator therapy | | | | |
| ADT | | | | |
| Degarelix | continuously, 1 × monthly | 12 | 1 | 12 |
| 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 |

Usage and consumption:

| Designation of the therapy | Dosage/ application | Dose/patient/treatment days | Consumption by potency/treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Enzalutamide | 160 mg | 160 mg | 4 × 40 mg | 365 | 1460 × 40 mg |
| Appropriate comparator therapy | | | | | |
| ADT | | | | | |
| Degarelix | 80 mg | 80 mg | 1 × 80 mg | 12 | 12 × 80 mg |
| Buserelin | 9.45 mg | 9.45 mg | 1 × 9.45 mg | 4 | 4 × 9.45 mg |
| Goserelin | 10.8 mg | 10.8 mg | 1 × 10.8 mg | 4 | 4 × 10.8 mg |
| Leuprorelin | 11.25 mg | 11.25 mg | 1 × 11.25 mg | 4 | 4 × 11.25 mg |
| Triptorelin | 22.5 mg | 22.5 mg | 1 × 22.5 mg | 2 | 2 × 22.5 mg |

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130 a 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.

**Costs of the medicinal product:**

| Designation of the therapy | Package 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 | | | | | |
| Enzalutamide 40 mg | 112 FCT | € 3,336.07 | € 1.77 | € 0.00 | € 3,334.30 |
| Degarelix 80 mg | 3 PSI | € 556.97 | € 1.77 | € 31.02 | € 524.18 |
| Buserelin 9.45 mg three-month implant | 2 PS | € 1,001.96 | € 1.77 | € 56.30 | € 943.89 |
| Goserelin 10.8 mg three-month implant | 2 IMP | € 987.74 | € 1.77 | € 55.49 | € 930.48 |
| Leuprorelin 11.25 mg three-month implant | 2 IMP | € 712.09 | € 1.77 | € 86.93 | € 623.39 |
| Triptorelin 22.5 mg | 1 DSS | € 920.37 | € 1.77 | € 51.66 | € 866.94 |

| Designation of the therapy | Package size | Costs (pharmacy sales price) | Rebate Section 130 SGB V | Rebate Section 130a SGB V | Costs after deduction of statutory rebates |
|---|---|---|---|---|---|
| Appropriate comparator therapy | | | | | |
| Degarelix 80 mg | 3 PSI | € 556.97 | € 1.77 | € 31.02 | € 524.18 |
| Buserelin 9.45 mg three-month implant | 2 PS | € 1,001.96 | € 1.77 | € 56.30 | € 943.89 |
| Goserelin 10.8 mg three-month implant | 2 IMP | € 987.74 | € 1.77 | € 55.49 | € 930.48 |
| Leuprorelin 11.25 mg three-month implant | 2 IMP | € 712.09 | € 1.77 | € 86.93 | € 623.39 |
| Triptorelin 22.5 mg | 1 DSS | € 920.37 | € 1.77 | € 51.66 | € 866.94 |
| Abbreviations: PS = prefilled syringes; FCT = film-coated tablets; PSI = powder and solvent for solution for injection; IMP = implant; DSS = dry substance with solvent | | | | | |

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 October 2020

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 assessed 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 standard expenditure in the course of the treatment are not shown.

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

## 3. Bureaucratic costs

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 8 August 2017, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 14 May 2020, the pharmaceutical company submitted a dossier for the benefit assessment of enzalutamide to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 5, sentence 2 VerfO.

By letter dated 14 May 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient enzalutamide.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 August 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 17 August 2020. The deadline for submitting written statements was 7 September 2020.

The oral hearing was held on 21 September 2020.

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 were discussed at the session of the subcommittee on 27 October 2020, and the proposed resolution was approved.

On 5 November 2020, the Federal Joint Committee (G-BA) resolved by written statement to amend the Pharmaceuticals Directive.

The patient representatives support the resolution.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee on Medicinal Products | 8 August 2017 | Determination of the appropriate comparator therapy |
| Working group Section 35a | 15 September 2020 | Information on written statements received; preparation of the oral hearing |
| Subcommittee on Medicinal Products | 21 September 2020 | Conduct of the oral hearing |
| Working group Section 35a | 29 September 2020<br>13 October 2020<br>20 October 2020 | Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure |
| Subcommittee on Medicinal Products | 27 October 2020 | Concluding discussion of the draft resolution |
| Plenum | 5 November 2020 | Written resolution on the amendment of Annex XII of the AM-RL |

Berlin, 5 November 2020

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

Prof. Hecken