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 Apalutamide (Reassessment after the Deadline: Non-metastatic Castration-resistant Prostate Cancer)

of 1 October 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 on the basis of proof 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 proof 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

The pharmaceutical company initially submitted a dossier for the early benefit assessment of the active ingredient apalutamide (Erleada®) on 24 January 2019. The resolution of 1 August 2019 passed by the G-BA in these proceedings was limited until 15 May 2020. This limitation was shortened to 1 April 2020 by a resolution of the G-BA dated 20 February 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 (Erleada®) 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 31 March 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 July 2020 on the website of the G-BA (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 apalutamide compared with the appropriate comparator therapy could be determined on the basis of the dossier of

the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has assessed 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 apalutamide.

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 apalutamide (Erleada®) in accordance with the product information

Erleada is indicated in adult men for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult men with non-metastatic castration-resistant prostate carcinoma (nmCRPC) who are at high risk of developing metastatic disease

Appropriate comparator therapy:

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.

[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.

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: Bicalutamide, darolutamide, flutamide, cyproterone acetate, enzalutamide, degarelix, buserelin, goserelin, leuprorelin, triptorelin, and estramustin (cytostatic drug).

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. A resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V has been passed on enzalutamide (resolution of 16 May 2019).

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 androgen deprivation therapy.

With regard to secondary hormone manipulation, in the benefit assessment for enzalutamide in the present therapeutic indication, there was no additional benefit compared with a wait-and-see approach while maintaining the existing conventional androgen deprivation (ADT) (resolution of 16 May 2019). The resolution was limited until 15 May 2020. A post-closure reassessment of the active ingredient enzalutamide will therefore be carried out simultaneously with the present benefit assessment procedure.

Since March 2020, the active ingredient darolutamide has also been available for the therapeutic indication being assessed. For darolutamide, a benefit assessment according to Section 35a SGB V is performed in parallel to this benefit assessment procedure. Darolutamide is another approved treatment option for patients in this therapeutic indication that is still very new. The therapeutic value can therefore not yet be conclusively assessed.

Thus, neither enzalutamide nor darolutamide can be considered as appropriate comparator therapies.

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 proof 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.

In the present therapeutic indication, conventional androgen deprivation therapy implies surgical castration or pharmacological castration with gonadotropic releasing hormone (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 apalutamide is assessed as follows:

Adult men with non-metastatic castration-resistant prostate carcinoma (nmCRPC) who are at high risk of developing metastatic disease

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 1 August 2019, the pharmaceutical company presented results of the SPARTAN study with a data cut-off from 1 December 2019. The implementation of this data cut-off was commissioned within the framework of the limitation of the initial resolution.

The SPARTAN study is a randomised, double-blind, placebo-controlled parallel group study. The ongoing study is being conducted in 234 study centres in 26 countries. A total of 1207 patients with non-metastatic castration-resistant prostate carcinoma at high risk of developing metastatic disease were included in the study. The presence of a high risk for the development of metastases was defined by a prostate-specific antigen (PSA) doubling time of ≤ 10 months.

Patients were randomised to either the apalutamide arm or the placebo 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 SPARTAN 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 74 years, most of them were from Europe (50%), and they had received their diagnosis of prostate cancer a median of approximately 8 years prior to randomisation. In approximately 97% of patients, androgen deprivation was achieved by medicinal castration using GnRH agonists or GnRH antagonists. Almost 6% of the patients had a prior orchiectomy.

The primary endpoint of the study was metastasis-free survival (MFS). In addition, the overall survival and endpoints of the categories morbidity (symptomatic progression, health status), health-related quality of life, and adverse events, among others, were surveyed.

Patients were treated until documented radiographic progression (development of remote metastases), withdrawal of consent, or occurrence of unacceptable toxicity. Once the therapy had been completed, there were no limitations regarding which type of follow-up treatment could be employed. In contrast to the initial assessment of apalutamide, which was based on the data cut-off of 19 May 2017, no information on the follow-up therapies administered is available for the 3rd data cut-off of 1 December 2019 on which the benefit assessment is now based.

Follow-up was performed for the endpoints overall survival and symptomatic progression every four months until death, lost to follow-up, or withdrawal of consent. The endpoints health status and health-related quality of life were monitored every four months up to a

maximum of twelve months after the occurrence of a progression event. For endpoints in the side effects category, follow-up was up to 28 days after treatment.

After the first a priori planned data cut-off of 19 May 2017, an amendment was made in the study to remove blinding and allow patients to switch treatment from the control arm to the apalutamide arm.

At the time of unblinding, 119 patients in the control arm were still receiving treatment. Of these, 76 patients (19%) switched to treatment with apalutamide. In the remaining 43 patients, disease progression before implementation of the amendment to the study protocol at the individual study centre (n = 23) or lack of patient consent (n = 12) were the main reasons for not switching to treatment with apalutamide.

Extent and probability of the additional benefit

Mortality

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

For the overall survival endpoint, there is a statistically significant difference between treatment arms in favour of apalutamide.

The median overall survival at the 3rd data cut-off was 66.10 months in the apalutamide arm and 58.68 months in the control arm. With regard to the resulting absolute difference of 7.42 months, uncertainties because of plateau formation in the corresponding section of the Kaplan-Meier curve in connection with a relatively small number of patients at risk must be taken into account when interpreting the results on overall survival.

Although apalutamide leads to an improvement in overall survival, the extent of the effect of apalutamide compared with a 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)

In the SPARTAN study, the MFS endpoint was defined as the time from randomisation to first occurrence of a confirmed radiographically detectable bone, soft-tissue bone metastasis, or death.

The MFS in the apalutamide arm is significantly longer than in the control arm.

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

The morbidity component was not calculated on the basis of symptoms but rather solely on the basis of imaging techniques (radiographic detection of metastasis) and thus solely on the basis of primarily asymptomatic findings and 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 non-metastatic castration-resistant high-risk prostate carcinoma 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 apalutamide 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.

An assessment as to whether the MFS can be considered a surrogate for overall survival cannot be made on the basis of the information provided by the pharmaceutical company in the dossier.

Time before initiation of cytotoxic chemotherapy

The time to initiation of cytotoxic chemotherapy endpoint was defined in the SPARTAN study as the time from randomisation to start of a new cytotoxic chemotherapy for prostate carcinoma.

For patients with non-metastatic castration-resistant high-risk 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 until the initiation of 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 significant uncertainties in the present case regarding the significance of the results for this endpoint. As a result, no conclusions can be drawn regarding additional benefit from the available data.

According to recommendations in the guidelines, any decision in the current 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 on the basis of 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, but this has not been made available, not having been collected in the SPARTAN study. The results for the endpoint time to initiation of cytotoxic chemotherapy are therefore not used in the present assessment.

Symptomatic progression

The combined endpoint symptomatic progression collected in the SPARTAN study, which is operationalised as time from randomisation to initial documentation, considers the following components:

- Development of a skeletal event (pathological fractures, compression of the spinal cord, or need for surgical intervention or radiotherapy of the bone)
- Pain progression or deterioration of disease-related symptoms with the need to initiate a new systemic cancer therapy
- Development of clinically significant symptoms because of locoregional tumour progression requiring surgical intervention or radiotherapy.

The patients in this therapeutic indication are in a palliative therapy situation. The control of symptoms and the maintenance of quality of life are therefore of particular importance. The endpoint of symptomatic progression, which shows a statistically significant advantage of apalutamide over a wait-and-see approach, is therefore considered patient-relevant.

However, the present operationalisation of the component "pain progression or deterioration of disease-related symptoms with the need to initiate a new systemic cancer therapy" requires that events of pain progression or deterioration of disease-related symptomatology are only included in the endpoint if a new systemic cancer therapy is initiated as a result of the event. Against the background of the long course of the disease in prostate cancer at this stage and the generally good general condition of the patients, the approach of defining a relevance threshold with regard to events of pain progression or the deterioration of disease-related symptoms can in principle be understood. However, patients in this therapeutic indication who experience such events without the need for a change of systemic therapy because they may be treated further with supportive, symptom-relieving measures are not systematically surveyed. In conclusion, it remains unclear how large the proportion of events not surveyed because of the chosen operationalisation is and how this influences the effect estimator of the combined endpoint, especially against the background of the present event rates for this component (9.6% vs 13.5%).

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

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

The pharmaceutical company presented responder analyses operationalised as time to deterioration and improvement by 7 or 10 points.

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.

Because the validation study in question has already been used in earlier assessment, in the present assessment, the G-BA nevertheless uses the responder analyses to assess the effects on the symptomatology.

There are no statistically significant differences in the time to deterioration.

Data on mean differences of EQ-5D VAS were not provided by the pharmaceutical company in the dossier.

In the overall consideration of the endpoint category morbidity, valid conclusions can be drawn only for a part of the existing endpoints or study results. Only for the endpoint symptomatic progression is there an advantage of treatment with apalutamide; this is because of the prolongation of the time until symptomatic progression. Based on the data available, this effect is evaluated as a moderate improvement in disease-related symptomatology that has not yet been achieved.

<u>Quality of life</u>

FACT-P

In the SPARTAN study, patients reported on their health-related quality of life via the FACT-P questionnaire. There is no statistically 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)

Almost all study participants experienced AE. The results 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 statistically significant differences between the treatment arms.

Specific AE

For the specific AE, an advantage in the endpoint "renal and urinary disorders (SOC, severe AE CTCAE grade ≥ 3)" is offset by disadvantages in other specific AE.

In detail, there are disadvantages for apalutamide compared with a wait-and-see approach in the endpoints "arthralgia" and "hypothyroidism" (each: PT, AE); "nervous system disorders", "infections and infestations", "Injury, poisoning, and procedural complications" (each: SOC, AE), and "skin and subcutaneous tissue disorders" (SOC, severe AE CTCAE grade ≥ 3).

In the overall assessment of the endpoint category of side effects, neither an advantage nor a disadvantage can be identified for apalutamide compared with the wait-and-see approach. Only the specific adverse events show differences. In detail, there are advantages and disadvantages for apalutamide compared with the wait-and-see approach.

Overall assessment

For the renewed benefit assessment of apalutamide for the treatment of adult men with non-metastatic castration-resistant prostate carcinoma (nmCRPC) who are at high risk of developing metastases, results for the endpoint categories mortality, morbidity, health-related quality of life, and side effects from the SPARTAN study are available.

In the ongoing study, apalutamide is compared 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 apalutamide 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 endpoint category morbidity, only some of the available endpoints or study results allow valid inferences. Only for the endpoint symptomatic progression is there a patient-relevant advantage of treatment with apalutamide. Based on the data available, this effect is evaluated as a moderate improvement in symptomatology that has not yet been achieved.

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

There is also no advantage or disadvantage of apalutamide in terms of side effects compared with a wait-and-see approach. There are significant differences only in the specific adverse events. In detail, there are both advantages and disadvantages.

In the overall view of the results on the patient-relevant endpoints, the advantage in overall survival and the improvement in clinical symptomatology are not offset by disadvantages in health-related quality of life and side effects.

As a result, for apalutamide for the treatment of adult men with non-metastatic castration-resistant prostate carcinoma (nmCRPC) who are at high risk of developing metastases, 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 SPARTAN 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 unblinding of the study or change of treatment, the endpoints symptomatic progression, therapy discontinuation because of adverse events, and the patient-reported endpoints are regarded as potentially highly biased.

There are also uncertainties with regard to the endpoint symptomatic progression because of the limitations regarding operationalisation.

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 apalutamide because of the expiry of the limitation of the resolution of 1 August 2019. The renewed benefit assessment is based on the results of the SPARTAN study with a data cut-off of 1 December 2019. The implementation of this data cut-off was commissioned within the framework of the limitation of the initial resolution.

Apalutamide is indicated for the treatment of adult men with non-metastatic castration-resistant prostate carcinoma (nmCRPC) who are at high risk of developing metastases.

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 SPARTAN study, patients were randomised to either the apalutamide 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 SPARTAN study are considered a sufficient approximation to the appropriate comparator therapy.

The improvement in overall survival achieved by apalutamide 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 endpoint category morbidity, the endpoint symptomatic progression shows a patient-relevant benefit from treatment with apalutamide.

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

In terms of side effects, there is also no advantage or disadvantage to apalutamide compared with the wait-and-see approach. The specific adverse events alone reveal both advantages and 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 resolution will be based on the information from the dossier of the pharmaceutical company. However, the patient numbers derived by the pharmaceutical company in the dossier is subject to uncertainties.

Accordingly, the calculation of the lower limit is mainly based on a database query of the UroCloud register[2] from 2018. Especially because of the high number of patients in the UroCloud[2] registry who are no longer actively documented, the lower limit can be assumed to be underestimated.

With regard to the number of patients in the upper limit, there are no patients with a duration of illness > 10 years in the 10-year prevalence used as a basis. The unit values can also not be conclusively assessed.

Overall, based on the underlying derivation, the number of patients can be expected to be in the upper range and beyond.

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 Erleada® (active ingredient: apalutamide) at the following publicly accessible link (last access: 16 September 2020):

https://www.ema.europa.eu/en/documents/product-information/erleada-epar-product-information_de.pdf

Treatment with apalutamide 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] https://www.urocloud.de/home.html

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 September 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				
Apalutamide	continuously, 1 × daily	365	1	365
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, 1 × every 6 months	2	1	2
Degarelix	continuously, 1 × monthly	12	1	12
Appropriate comparator therapy				
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

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Triptorelin	continuously, 1 × every 6 months	2	1	2
Degarelix	continuously, 1 × monthly	12	1	12

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					
Apalutamide	240 mg	240 mg	4 × 60 mg	365	1460 × 60 mg
ADT					
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
Degarelix	80 mg	80 mg	1 × 80 mg	12	12 × 80 mg
Appropriate comparator therapy					
ADT					
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
Degarelix	80 mg	80 mg	1 × 80 mg	12	12 × 80 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					
Apalutamide	112 FCT	€ 2,967.76	€ 1.77	€ 0.00	€ 2,965.99
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
Degarelix 80 mg	3 PSI	€ 556.97	€ 1.77	€ 31.02	€ 524.18
Appropriate comparator therapy					
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
Degarelix 80 mg	3 PSI	€ 556.97	€ 1.77	€ 31.02	€ 524.18
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 September 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 9 January 2018, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 31 March 2020, the pharmaceutical company submitted a dossier for the benefit assessment of apalutamide to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 5 VerfO.

By letter dated 31 March 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 apalutamide.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 June 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 1 July 2020. The deadline for submitting written statements was 22 July 2020.

The oral hearing was held on 10 August 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 22 September 2020, and the proposed resolution was approved.

At its session on 1 October 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	9 January 2018	Determination of the appropriate comparator therapy
Working group Section 35a	4 August 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	10 August 2020	Conduct of the oral hearing
Working group Section 35a	18 August 2020; 1 September 2020; 15 September 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	22 September 2020	Concluding discussion of the draft resolution
Plenum	1 October 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 1 October 2020

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

Prof. Hecken