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

of 1 August 2019

Contents

1. Legal basis

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

1st Approved therapeutic indications,

2nd Medical benefit,

3rd Additional medical benefit in relation to the appropriate comparator therapy,

4th Number of patients and patient groups for whom there is a therapeutically significant additional benefit

5th Treatment costs for statutory health insurance funds,

6th Requirement 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 shall pass a resolution 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 relevant date for the first placing on the market of the active ingredient apalutamide in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 February 2019. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1 number 1 VerfO on 24 January 2019.

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 2 May 2019, thus initiating the written statement procedure. An oral hearing was also held.

The G-BA came to a resolution on whether an additional benefit of 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, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5,

Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of apalutamide.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of apalutamide (Erleada®) in accordance with the product information

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

2.1.2 Appropriate comparator therapy

Adult men with non-metastatic castration-resistant prostate carcinoma (nm-CRPC) who are at high risk of developing metastases:

A monitoring 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 products 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. In addition to apalutamide, medicinal products containing the following active ingredients are approved for use in the therapeutic indication: bicalutamide, flutamide, cyproterone acetate, enzalutamide (anti-androgenic); degarelix (GnRH antagonist);

[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.

buserelin, goserelin, leuprorelin, triptorelin (GnRH agonists) and estramustine (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. 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 evaluating non-medicinal traetments such as interstitial brachytherapy for localised prostate cancer, and proton therapy for prostate cancer as new methods for diagnosis and treatment. Both evaluation 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.

This showed how limited the evidence is for the various therapeutic options. No relevant Cochrane reviews or systematic reviews were identified. The data basis supporting whether pharmacological androgen deprivation should be continued unaltered, modified, or discontinued to treat the indication is both qualitatively weak and contradictory. However, the current guidelines predominantly recommend a monitoring wait-and-see approach with continuation of androgen deprivation therapy.

With regard to secondary hormone manipulation, the benefit assessment for enzalutamide in the present therapeutic indication did not identify any additional benefit compared with a monitoring wait-and-see approach while retaining the existing conventional androgen deprivation (ADT) (resolution of 16 May 2019). For the remaining antiandrogens, there is no evidence of efficacy in clinically relevant endpoints. Chemotherapy is not recommended to treat non-metastatic castration-resistant prostate cancer.

On the basis of the available evidence, the G-BA considers the monitoring 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 treating the condition 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 mandate.

2.1.3 Extent and probability of the additional benefit

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

Hint for a minor additional benefit.

Justification:

For the benefit assessment, the pharmaceutical company submitted data from the SPARTAN pivotal authorisation study for the present therapeutic indication of apalutamide. This was a randomised, double-blind, placebo-controlled parallel group study.

A total of 1207 patients with non-metastatic castration-resistant prostate carcinoma at high risk of developing metastases were included in the study and assigned either to the apalutamide arm or to the monitoring wait-and-see approach (placebo) 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. The presence of a high risk for the development of metastases was defined by a prostate-specific antigen (PSA) doubling time of ≤ 10 months. 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 previous orchiectomy.

The primary endpoint of the study was metastasis-free survival (MFS), while patient-relevant secondary endpoints were overall survival, symptomatic progression, health status, health-related quality of life, and adverse events.

Patients were treated until documented radiographic progression (development of distant 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. At the time of this data cut-off, 21.7% of patients in the apalutamide arm and 55.4% of patients in the control arm received systemic follow-up therapy. The most frequent follow-up therapies administered in the study were abiraterone acetate (71.4% and 72.5%, respectively; related to patients who received follow-up therapy) and ensalutamide (11.4% and 12.6%, respectively; related to patients who received follow-up therapy).

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.

The study started in September 2013 and is ongoing, and is being conducted at 234 centres in a total of 26 countries.

In the dossier, the pharmaceutical company presents the results of the SPARTAN study for the first a priori planned data cut-off of 19 May 2017. After this data cut-off, the blinding in the study was lifted, and a change of treatment of the patients from the control arm to the apalutamide arm was allowed.

As part of the written statement procedure, the pharmaceutical company submitted a second data cut-off for the SPARTAN study. However, this data cut-off, which was not planned a priori, is not to be assumed to have been produced in ignorance of the results. In the written statement procedure, the pharmaceutical company states that the subsequent data cut-off took place on 3 April 2019 and would include data up to and including the clinical cut-off of 1 February 2019. Furthermore, the data cut-off was made after a formal adaptation of the study protocol on 3 March 2019 and the statistical analysis plan on 4 March 2019. It is unclear at what time the data cut-off actually took place because the pharmaceutical company does not use the terms data cut-off and clinical cut-off synonymously. However, because the pharmaceutical company also referred to the date 19 May 2017 for the first data cut-off as the clinical cut-off in the written statement and the date 3 April 2019 as the database lock in the oral hearing, it is to be assumed that the date of the subsequent data cut-off is 1 February 2019 and that the date of the database lock is 3 April 2019. According to the adapted study

protocol and statistical analysis plan, this second data cut-off should be made after the occurrence of 65% of the number of events planned for the final analysis of overall survival. The rationale for this criterion, which gives the date for the second data cut-off (1 February 2019), is not apparent from the written statement procedure of the pharmaceutical company or from the oral hearing. Moreover, the study protocol and the statistical analysis plan were only adapted after this date.

Furthermore, as previously described, the SPARTAN study was unblinded on 22 July 2017 after the first data cut-off on 19 May 2017. Patients who were still under treatment in the placebo arm were then able to switch to treatment with apalutamide. According to the pharmaceutical company, the remaining 76 patients (19%) completed this change of therapy. According to the study documents, 119 patients were still under treatment at the time of the first data cut-off in the placebo arm. The difference results in 43 additional patients for whom no information is available.

From the point of view of the G-BA, there are therefore significant uncertainties for this second data cut-off. In particular, it cannot be ruled out that the decision to carry out the data cut-off was made on the basis of results. The benefit assessment is thus carried out on the basis of the first, pre-specified data cut-off dated 19 May 2017, which also formed the basis for the marketing authorisation.

Extent and probability of the additional benefit

Mortality

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

As of 19 May 2017, a total of 104 patients had died, 62 in the intervention arm and 42 in the comparator arm. As a result of the 2:1 randomisation, this represents respectively 7.9% and 10.5%. The median survival time has not yet been obtained in both arms, and there is no statistically significant difference in overall survival (hazard ratio (HR): 0.70; [95% confidence interval (CI): 0.47; 1.04]; p value 0.076).

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.

In the intervention group there was a statistically significant increase in median MFS of 24.81 months compared with the control group (median of 40.51 vs. 15.70 months; HR: 0.30; [95% CI: 0.24; 0.36]; $p < 0.0001$;

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.

The operationalisation of the study precludes direct symptomatic assessment of disease metastasis by patients, and distinguishing between symptomatic and asymptomatic metastases is therefore not possible. As 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.

The extent to which metastasis-free survival prolonged with apalutamide translates into prolonged patient survival cannot be assessed based on the data available – the final analysis of the overall survival endpoint is still pending.

As a result, it is highly uncertain whether the results for this endpoint can be used to evaluate patient-relevant benefit, and, for this reason, the endpoint MFS is not taken into account in the present assessment.

With regard to the question of whether MFS can be regarded as a surrogate for overall survival, the analyses submitted by the pharmaceutical company in the dossier do not provide sufficient evidence that MFS is a valid surrogate endpoint for overall survival in the present indication.

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 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, it is clearly uncertain whether the results for this endpoint are meaningful, and, 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 an individual patient 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 findings for the time to initial subsequent chemotherapy endpoint are therefore not included in this 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 monitoring 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 symptoms 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 recorded. In conclusion, it remains unclear how large the proportion of events not recorded because of the chosen operationalisation is and how this influences the effect estimator of the combined endpoint, especially against the background of the low event rates for this component (4.3% vs 7.0%).

Health status (EQ-5D visual analogue scale)

In order to assess the health status of the study patients, the pharmaceutical company presents responder analyses for the time up to deterioration by ≥ 7 points and by ≥ 10 points compared with baseline.

Instead of the responder analyses, the IQWiG dossier evaluation uses the evaluation of the mean change with the result for cycle 13 (corresponds to about one year after the start of treatment). The difference between the study arms is not statistically significant regarding mean difference.

The IQWiG classifies the study on which the derivation of the MID for the responder analyses is based (Pickard et al., 2007) as unsuitable to prove the validity of the MID. This is justified on the one hand by the fact that the work mentioned does not contain a longitudinal study for the determination of MID, which is assumed in the current scientific discussion for the derivation of a valid MID. In addition, the IQWiG does not consider the ECOG-PS and FACT-G anchors used in the study to be suitable for the derivation of MID.

Against the background that responder analyses based on a MID for a clinical assessment of effects have general advantages compared with an analysis of standardised mean value differences and taking into account that the validation study in question has already been used in previous evaluations, the responder analyses are nevertheless used by the G-BA in the present assessment to assess the effects on the symptoms.

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

Summary

In summary, only some of the available endpoints and study results would permit valid inferences to be made on morbidity. Only for the endpoint symptomatic progression is there an advantage of treatment with apalutamide. Based on the data available, this effect is evaluated as a moderate improvement in disease-related symptoms that has not yet been achieved.

Quality of life

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. 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 only on a supplementary basis.

Side effects

Adverse events (AE) in total

In the SPARTAN study, approx. 97% of patients in the intervention arm and approx. 93% of patients in the comparator arm experienced an adverse event. The results for the endpoint "total adverse events" are only presented on a supplementary basis.

Serious AE

In the SPARTAN study, approx. 25% of patients in the intervention arm and approx. 23% of patients in the comparator arm experienced a serious adverse event. The event time analysis showed no statistically significant difference.

Severe AE (CTCAE grade ≥ 3)

In the SPARTAN study, approx. 46% of patients in the intervention arm and approx. 34% of patients in the comparator arm experienced a severe adverse event (CTCAE grade ≥ 3). The event time analysis showed no statistically significant difference.

Therapy discontinuation because of AE

In the case of therapy discontinuation because of AE, no statistically significant difference between the treatment groups was found in the event time analysis.

Specific AE

There is a statistically significant advantage for apalutamide over a monitoring wait-and-see approach in renal and urinary disorders (SOC, severe AEs). On the other hand, there are statistically significant disadvantages for apalutamide compared with the monitoring wait-and-see approach with regard to nervous system disorders (SOC, AE), arthralgia (PT, AE), hypothyroidism (PT, AE), skin and subcutaneous tissue disorders (SOC, severe AE), general disorders and administration site conditions (SOC, severe AE) as well as injury, poisoning, and procedural complications (SOC, SAE).

As an overall finding in the adverse event endpoint category, only specific adverse events were shown to be statistically significant. The finding is that apalutamide has both benefits and detriments compared with the monitoring wait-and-see approach.

Overall assessment

For the benefit assessment of apalutamide for the treatment of adult men with non-metastatic castration-resistant prostate carcinoma who are at high risk of developing metastases, the SPARTAN study provides results on overall survival, morbidity, health-related quality of life, and side effects.

In the endpoint category mortality, there is no statistically significant difference in overall survival between the study arms. The study is ongoing, and further data for the overall survival are pending. An additional benefit of apalutamide is not proven for overall survival.

In the morbidity endpoint, only some of the available endpoints or study results would permit valid inferences to be made. Only for the endpoint symptomatic progression is there an advantage of treatment with apalutamide. Based on the data available, this effect is evaluated as a moderate improvement in symptoms that has not yet been achieved. With regard to the "metastasis-free survival" endpoint, there are considerable uncertainties as to the significance of the results on patient-relevant benefit, and, for this reason, this endpoint is not included in the current assessment. Similarly, the results for the endpoint "time to the initiation of cytotoxic chemotherapy" do not allow any valid conclusions to be drawn on the additional benefit of apalutamide, in particular because essential information on how decisions were made whether or not to employ chemotherapy are not available.

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

In the adverse event endpoint category, only specific adverse events were shown to be statistically significant. There are both benefits and detriments, which have no influence on the overall assessment of the additional benefit, taking into account the extent and clinical significance.

Overall, the G-BA found a minor additional benefit for apalutamide compared with the appropriate comparator therapy based on the advantage at the endpoint symptomatic progression.

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.

At the endpoint level, the risk of bias for the endpoints overall survival and therapy discontinuation because of AE is considered low. Uncertainties relevant to the assessment with regard to the reliability of data at the endpoint symptomatic progression result from the low event rates in connection with the aforementioned limitations with regard to operationalisation.
Further uncertainties arise from the fact that, as also presented by medical experts in the present written statement procedure, the transferability of the study results to the German health care context cannot be conclusively assessed. Thus, there is no information available regarding the circumstances surrounding the initiation of androgen deprivation therapy that would permit a conclusive assessment of the representativeness of the study population for the German health care context.
In the overall view, the uncertainties described justify a classification of the reliability of data as a hint for an additional benefit.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of apalutamide has its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter,

the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In this case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment pursuant to Section 35a, paragraph 1 SGB V.

The overall survival data from the SPARTAN study available for this assessment are inconclusive because of the limited number of occurrences at the time of the data cut-off. With regard to the second data cut-off submitted with the written statement of the pharmaceutical company, there are significant uncertainties as explained above. This can therefore not be used for the benefit assessment. The present limitation is intended to enable a more meaningful data basis on overall survival as well as other patient-relevant endpoints to be included in the benefit assessment in a timely manner. The final data cut-off of the SPARTAN study, which was planned a priori, seems less suitable for this purpose because a high bias of the results can be assumed because of the change of treatment from placebo to apalutamide permitted after the first data cut-off.

Conditions of the limitation:

For the renewed benefit assessment, a data cut-off of the SPARTAN study is to be carried out on 1 December 2019, and a separate report on the results of the study for this data cut-off is to be submitted. This report should completely map the data available for the data cut-off for all patient-relevant endpoints.

For this purpose, the G-BA considers a limitation of the resolution until 15 May 2020 to be appropriate.

In accordance with Section 3 paragraph 1 number 5 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of the drug apalutamide shall recommence when the deadline has expired. For this purpose, the pharmaceutical manufacturer must submit a dossier to the G-BA at the latest on the day of expiry of the deadline to prove the extent of the additional benefit of apalutamide compared with an appropriate comparator (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO). If the dossier is not submitted or submitted incompletely, the G-BA may come to the finding that an additional benefit is not proven.

The possibility that a benefit assessment for apalutamide can be carried out at an earlier point in time for other reasons (*cf.* Chapter 5, Section 1 paragraph 2 VerfO) remains unaffected by this.

2.1.5 Summary of the assessment

The present assessment concerns the benefit assessment of the new active ingredient apalutamide with the therapeutic indication:

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

The appropriate comparator therapy was deemed to be a monitoring wait-and-see approach while maintaining the existing conventional androgen deprivation.

The pharmaceutical manufacturer has presented the results of the randomised, double-blind, placebo-controlled SPARTAN study, in which apalutamide was compared with a monitoring wait-and-see approach to support the benefit assessment. In both study arms, patients also received, or continued to receive, androgen deprivation therapy with a GnRH agonist or antagonist, unless they had already undergone orchiectomy.

The data on overall survival are preliminary, and therefore no assessment of the effectiveness can as yet be drawn for the mortality endpoint category. Based on the available data, there is no statistically significant difference in overall survival between the study arms. The study is ongoing, and further data for the overall survival are pending.

In the morbidity endpoint, only some of the available endpoints or study results would permit valid inferences to be made. However, the uncertainties of the results for the endpoints "metastasis-free survival" and "time to initiation of cytotoxic chemotherapy" were so significant that they were not considered in the present assessment (i.e. it was not possible to derive any additional benefit from them). Only for the endpoint symptomatic progression is there an advantage of treatment with apalutamide. Based on the data available, this effect is evaluated as a moderate improvement in symptoms that has not yet been achieved.

In the health-related quality of life endpoint category, it has not been proven that treatment with apalutamide is beneficial or detrimental.

In the adverse event endpoint category, only specific adverse events were shown to be statistically significant. There are both benefits and detriments, which have no influence on the overall assessment of the additional benefit, taking into account the extent and clinical significance.

The resolution is limited until 15 May 2020, in particular because of the still inconclusive data on overall survival.

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 patient numbers stated by the pharmaceutical company in the dossier are essentially based on a database query of the UroCloud registry[2] from 2018.

On one hand, not all query steps can be traced in detail. On the other hand, it remains unclear whether the database available in the registry is sufficiently representative of the proportion of patients with non-metastasised high-risk prostate carcinoma against the background of a high proportion of patients with an unknown risk profile and a high number of patients no longer actively documented in the database. Furthermore, the pharmaceutical company exclusively considers patients who enter the non-metastatic, castration-resistant stage within one year. This leads to an underestimation because patients who remain in this disease stage for longer than one year are not taken into account. Ultimately, the assumption of one additionally ill patient per year within the UroCloud registry for determining the upper limit indicated in the dossier cannot be reconstructed.

In order to enable a consistent consideration of patient numbers in view of these serious uncertainties, taking into account the most recent resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the present therapeutic indication, the relevant information from the resolution on enzalutamide of 16 May 2019 is taken over for this resolution.

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: 10 May 2019):

[2] https://www.urocloud.de

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

Only specialists in internal medicine, haematology and oncology with experience treating patients with prostate cancer, and specialists in urology and other doctors from other specialisms participating in the oncology agreement may initiate and monitor treatment with apalutamide.

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 July 2019).

Treatment period:

If no maximum treatment duration is specified in product information, a duration of one year is assumed, even if the actual duration of treatment varies between patients and/or is shorter on average.

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	continuous, 1 x daily	365	1	365
Buserelin	continuous, 1 x every 3 months	4	1	4
Goserelin	continuous, 1 x every 3 months	4	1	4
Leuprorelin	continuous, 1 x every 3 months	4	1	4
Triptorelin	continuous, 1 x every 6 months	2	1	2
Degarelix	continuous, 1 x monthly	12	1	12
Appropriate comparator therapy				
Buserelin	continuous, 1 x every 3 months	4	1	4
Goserelin	continuous, 1 x 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	continuous, 1 x every 3 months	4	1	4
Triptorelin	continuous, 1 x every 6 months	2	1	2
Degarelix	continuous, 1 x monthly	12	1	12

Usage and consumption:

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					
Apalutamide	240 mg	240 mg	4 × 60 mg	365	1460 × 60 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
Degarelix	80 mg	80 mg	1 × 80 mg	12	12 × 80 mg
Appropriate comparator therapy					
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:

To facilitate comparability, the pharmaceutical costs were approximated both on the basis of the pharmacy sales price level and also the price less 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 pharmaceutical costs were then calculated on the basis of the costs per pack less 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	€ 4,143.81	€ 1.77	€ 233.38	€ 3,908.66
Buserelin 9.45 mg three-month implant	2 PS	€ 1,027.81	€ 1.77	€ 56.30	€ 969.74
Goserelin 10.8 mg three-month implant	2 IMP	€ 1,013.23	€ 1.77	€ 55.49	€ 955.97
Leuprorelin 11.25 mg three-month implant	2 IMP	€ 730.45	€ 1.77	€ 86.93	€ 641.75
Triptorelin 22.5 mg	1 DSS	€ 944.11	€ 1.77	€ 51.66	€ 890.68
Degarelix 80 mg	3 PSI	€ 563.58	€ 1.77	€ 30.59	€ 531.22
Appropriate comparator therapy					
Buserelin 9.45 mg three-month implant	2 PS	€ 1027.81	€ 1.77	€ 56.30	€ 969.74
Goserelin 10.8 mg three-month implant	2 IMP	€ 1,013.23	€ 1.77	€ 55.49	€ 955.97
Leuprorelin 11.25 mg three-month implant	2 IMP	€ 730.45	€ 1.77	€ 86.93	€ 641.75
Triptorelin 22.5 mg	1 DSS	€ 944.11	€ 1.77	€ 51.66	€ 890.68
Degarelix 80 mg	3 PSI	€ 563.58	€ 1.77	€ 30.59	€ 531.22
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 July 2019

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 usual 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.

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 9 January 2018.

On 24 January 2019, 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 1 VerfO.

By letter dated 24 January 2019 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 April 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 1 May 2019. The deadline for submitting written statements was 23 May 2019.

The oral hearing was held on 11 June 2019.

By letter dated 12 June 2019, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 11 July 2019.

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 statements received and the oral hearing were discussed at the session of the subcommittee on 23 July 2019, and the proposed resolution was approved.

At its session on 1 August 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	9 January 2018	Determination of the appropriate comparator therapy
Working group Section 35a	5 June 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	11 June 2019	Conduct of the oral hearing Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 June 2019 3 July 2019 17 July 2019	Consultation on the dossier assessment by the IQWiG and the evaluation of the written statement procedure

Subcommittee Medicinal products	23 July 2019	Concluding discussion of the proposed resolution
Plenum	1 August 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 1 August 2019

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

Prof Hecken