Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Appendix XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients in Accordance with Section 35a SGB V Enzalutamide (New Therapeutic Indication: Non-Metastatic Castration-Resistant High-Risk Prostate Cancer)

From 16. May 2019

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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, assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical manufacturer, which, at the latest by the time it is placed on the market for the first time, must be submitted in computerised form to the G-BA along with information on all clinical trials the pharmaceutical manufacturer has conducted or commissioned and the marketing authorisation of new therapeutic indications of the medicinal product, in particular including the following information:

1st approved therapeutic indications,

2nd medicinal benefit,

3rd additional medicinal benefit compared to the appropriate comparator therapy,

4th number of patients and patient groups with an established therapeutic benefit,

5th costs of therapy for statutory health insurance funds, and

6th requirements for 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 decide 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 active ingredient enzalutamide was priced for the first time on 1 September 2013 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 23 October 2018, enzalutamide was approved for a new therapeutic indication:

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

The new therapeutic indication is classified as a major variation of type II according to Annex 2 number 2 letter a of Commission Regulation (EC) No. 1234/2008 of 24 November 2008, concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 Dec. 2008, p. 7).

On 19 November 2018, i.e. within four weeks of the pharmaceutical manufacturer being informed of the authorisation of a new therapeutic indication, the pharmaceutical manufacturer submitted in due time a dossier pursuant to Section 4, paragraph 3, number 2 of the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA covering the active ingredient enzalutamide and its new therapeutic indication (non-metastatic castration-resistant high-risk prostate cancer).

The G-BA commissioned the IQWiG to assess the dossier. The benefit assessment was published on 1 March 2019 on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. An oral hearing was also held.

The G-BA made its decision on the question of whether an additional benefit of enzalutamide compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical manufacturer, on the evaluation of the dossier prepared by the IQWiG (IQWiG no. A18-80), on the on the comments submitted in the written and oral hearings, and on the addendum prepared by the IQWiG on the benefit assessment. To determine the extent of the additional benefit, the G-BA evaluated the data supporting the determination of an additional benefit on the basis of their (qualitative) therapeutic relevance, following the criteria stipulated in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 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™) according to the technical 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

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 regarded, according to the generally accepted state of medical knowledge, as an appropriate therapy in the therapeutic indication (Section 12 SGB V), and should preferably be 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 efficiency principle.

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. A medicinal product administered as a comparator therapy must always be authorised for the intended therapeutic indication.
2. If the comparator therapy is a non-medicinal treatment, this must be available under SHI insurance.
3. Comparator therapies should preferably be those drugs or non-medicinal treatments whose benefit to patients has already been determined by the G-BA.
4. The comparator therapy should, according to the generally accepted state of medical knowledge, be indicated for the intended therapeutic indication.

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

On 1. In addition to enzalutamide, drugs containing the following active ingredients are approved for use in the therapeutic indication: bicalutamide, flutamide, cyproterone acetate (anti-androgenic); degarelix (GnRH antagonist); 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. To date, the G-BA has not yet passed any resolutions on drugs that can be employed for the intended therapeutic indication. All G-BA resolutions on preliminary benefit assessment, as defined in Section 35a SGB V for the indication "prostate cancer", were passed for other disease stages, and they are, therefore, irrelevant to identifying an appropriate comparator therapy.

The G-BA is evaluating non-pharmacological therapies such as interstitial brachytherapy for localized 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 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.

No evidence exists as to the efficacy of secondary hormone manipulation (e.g. with anti-androgens) to achieve clinically relevant endpoints in treatment. 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 treating adult men with non-metastatic castration-resistant prostate cancer.

Conventional androgen deprivation therapy (ADT) in treating the condition implies surgical castration or pharmacological castration with GnRH agonists or GnRH antagonists.

The findings established in Annex XII should not be construed as constraining the scope of treatment available to medical practitioners tasked with treatment.

2.1.3 Extent and probability of the additional benefit

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

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

No additional benefit has been established.

Justification:

The pharmaceutical manufacturer's benefit assessment of the value of enzalutamide for treating the new therapeutic indication draws in the dossier on the results of the PROSPER approval study. This was a randomised, double-blind, placebo-controlled parallel group study.

A total of 1401 patients with non-metastatic castration-resistant high-risk prostate cancer were included in the study and assigned at a ratio of 2:1, either to an enzalutamide arm or to a purely monitoring arm (placebo). 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 prostate cancer was categorised as high-risk on the basis of a doubling of prostate-specific antigen (PSA) within the prior 10 months. 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 study's primary endpoint was metastasis-free survival (MFS), while patient-relevant secondary endpoints were mortality, pain, health status, health-related quality of life and side effects.

Patients were treated in accordance with the doctor's recommendation or according to the patient's own wishes until the disease progressed, chemotherapy was initiated, androgen receptor inhibitors or other trial drugs were administered, or until withdrawal from treatment.

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 (7.6% and 20%) and abiraterone acetate (7.0% and 28%).

Follow-up was performed to ascertain overall survival until death and adverse events 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 study started in November 2013 and is ongoing, and is being conducted at 254 centres in a total of 32 countries. The current benefit assessment is based on all endpoints, except for overall survival, on an a priori planned data cut-off of 28 June 2017 to analyse the MFS endpoint. For the overall survival endpoint on the results of the planned interim analysis of 31 May 2018. A further interim analysis of the overall survival endpoint and the final data cut-off on overall survival is pending.

Extent and probability of the additional benefit

Mortality

In the PROSPER study, overall survival was defined as the time from randomisation to death from any cause.
As of 31 May 2018, a total of 288 patients had died, 184 in the intervention arm and 104 in the comparator arm. As a result of the 2:1 randomisation, this represents respectively 19.7% and 22.2%. 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): 0.83; [95% confidence interval (CI): 0.65; 1.06]; p-value 0.134).

A further interim analysis and the overall survival data cut-off from the ongoing study are still to be completed.

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 evidence of radiographic progression. The MFS endpoint was assessed on the basis of radiographic assessment of bone metastases and soft tissue metastases.

In the intervention group there was a statistically significant increase in median MFS of 21.9 months compared to the control group (median of 36.6 vs. 14.7 months; HR: 0.29; [95% CI: 0.24; 0.35]; p-value < 0.001).

In the study's operationalisation, 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 calculated on the basis of symptoms, but solely on the basis of imaging techniques (radiologically determined disease progression according to the RECIST criteria), and thus solely on the basis of primarily asymptomatic findings rather than directly patient-relevant findings.

The study's operationalisation 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 presented data on the MFS endpoint suggest that enzalutamide delays metastasis but does not prevent it, although no conclusions can be drawn regarding those patients in the study who died before metastasis.

At present, it is impossible to assess the extent to which the prolongation of metastasis-free survival resulting from enzalutamide will also contribute to improved patient survival – further analyses on the overall survival endpoint have yet to be carried out.

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 "metastasis-free survival" (MFS) is not taken into account in the present assessment.

Regarding the claims made in the pharmaceutical manufacturer's dossier that MFS can be regarded as a surrogate for the patient-relevant overall survival endpoint, there is insufficient evidence that this is the case for the indication under consideration.

Time to commencement of cytotoxic chemotherapy

The time to commencement 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. The median time to the commencement of cytotoxic chemotherapy in the intervention arm was extended by 4.1 months. This difference is statistically significant.

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 beginning 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 a patient-specific 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 PROSPER study. The findings for the time to initial subsequent chemotherapy endpoint are therefore not included in this evaluation.

Health status (EQ-5D visual analogue scale)

To demonstrate benefit assessment, the pharmaceutical manufacturer has submitted responder analyses in the dossier on "time to first deterioration" and "time to prolonged deterioration" corresponding, respectively, to ≥ 7 points and ≥ 10 points. In the pharmaceutical manufacturer's statement, the indicated operationalisations were extended with the submission of additional assessments, resulting in a deterioration of ≥ 12 points. In addition, the pharmaceutical manufacturer also submitted additional assessments in its statement for "time to definite deterioration" each by ≥ 7 points, ≥ 10 points and ≥ 12 points, in each case with and without censorship of deaths.

Instead of responder analyses, the IQWiG used mean change analysis in its dossier assessment. The difference between the study arms is not statistically significant regarding 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. One reason given by the IQWiG was that this paper did not include a longitudinal study on determining the MID, which in the context of the current scientific debate is considered a prerequisite for deriving a valid MID. In addition, the IQWiG does not consider the anchors ECOG-PS and FACT-G used in the study to be suitable for deriving the MID.

In view of the fact that responder analyses based on MID have general advantages over an analysis of standardised mean value 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.

Due to the steep decline in response rates, differing between study arms, and a significant proportion of patients missing from the evaluation, the results for "time to prolonged deterioration" and "time to definitive deterioration" are highly susceptible to bias.

Only data on "time to first deterioration" are, therefore, used for the benefit assessment. For this data both response criteria (≥ 7 points and ≥ 10 points) reveal enzalutamide to be associated with statistically significant benefits, compared to the monitoring wait-and-see approach. In the intervention arm, the median time to deterioration of health status was extended by 3.6 months (MID ≥ 7 points): median value of 11.1 vs. 7.5 months; HR: 0.83; [95% CI: 0.71; 0.97]; p = 0.019 respectively MID ≥ 10 points: median value of 14.6 vs. 11.0 months; HR: 0.79; [95% CI: 0.67; 0.93]; p-value = 0.004).

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. In its dossier on benefit assessment, the pharmaceutical manufacturer presented data on mean value differences for item 3 ("strongest pain"), item 9a–g ("pain impairment") and items 3 to 6 ("mean pain intensity"). It also presented responder analyses on "time to first deterioration" and "time to persistent deterioration" for item 3, each at ≥ 2 points. Such responder analyses are presented as showing no statistically significant difference for the endpoints "strongest pain" and "impairment by pain" between the treatment groups. 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 on a supplementary basis.

EORTC-QLQ-PR25

The symptoms of the patients in the PROSPER study were evaluated by means of the EORTC QLQ-PR-25 prostate-cancer-specific questionnaire, which comprises, in total, four symptom scales. According to the authors, this questionnaire is only valid when evaluated in combination with findings from the core questionnaire EORTC QLQ-C30. However, this questionnaire was not recorded in the study. Taken in isolation, QLQ-PR25 is, therefore, presented as being invalid as a comprehensive description of symptoms. This applies equally to both functional scales of QLQ-PR25. For this reason, the results for EORTC QLQ-PR25 were not included in the current benefit assessment.

In summary, only some of the available endpoints and study results would permit valid inferences to be made on morbidity. As a result, the only endpoint that might allow statistically significant differences to be established in favour of enzalutamide is the health status endpoint, as measured by the EQ-5D VAS scale "time to first deterioration". 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 conclude 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.

For the reasons mentioned above, responder analysis for "time to first deterioration" was also employed to determine an overall score, with no statistically significant differences being found between the treatment groups.

Only the FACT-P total score was considered in assessing the additional benefit, as this provides a comprehensive overview of the data on patients' health-related quality of life. FACT-P's individual sub-scales are therefore presented only on a supplementary basis.

Side effects

Adverse events (AEs) in total

In the PROSPER study, approx. 87% of patients in the intervention arm and approx. 77% of patients in the comparison arm experienced an adverse event. The results for the endpoint "total adverse events" are only presented on a supplementary basis.

Serious AEs

In the PROSPER study, approx. 22% of patients in the intervention arm and approx. 18% of patients in the comparison arm experienced a serious adverse event; these differences are not statistically significant.

Severe AE (CTCAE grade ≥ 3)

In the PROSPER study, approx. 30% of patients in the intervention arm and approx. 23% of patients in the comparison arm experienced a severe adverse event (CTCAE grade ≥ 3); these differences are not statistically significant.

Termination of therapy due to AEs

There was no statistically significant difference between the treatment groups for termination of therapy due to AEs.

Specific AEs

Compared to the monitoring wait-and-see approach, enzalutamide was found to have statistically significant benefits with regard to renal and urinary disorders (SOC, severe AEs) and urinary tract infections (PT, AEs). For urinary tract infections, the Gleason Score (p-value = 0.033) provided evidence of an effect modification. In the patient subgroup with a Gleason Score ≤ 7, there was a statistically significant difference in favour of enzalutamide compared to the monitoring wait-and-see approach, whereas in the population with a Gleason Score ≥ 8 there was no statistically significant difference between the treatment groups. In contrast, statistically significant detriments of enzalutamide were established compared to the monitoring wait-and-see approach for disorders of the nervous system (SOC, severe AEs), fatigue (PT, severe AEs), loss of appetite (PT, AEs), vascular diseases (SOC, AEs) and falls (PT, AEs). The findings on falls showed evidence of an effect modification due to patient age (p-value = 0.006). For the subgroup of patients aged < 75 years there was no statistically significant difference between the treatment groups, while for the population aged ≥ 75 years there was a statistically significant difference disadvantageous to enzalutamide compared to the monitoring wait-and-see approach.

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

Overall assessment / conclusion

The benefit assessment of enzalutamide for 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.

In the mortality endpoint category, the available data do not reveal a statistically significant difference between the study arms in overall survival. A further interim analysis and the overall survival data cut-off from the ongoing study are still to be completed. Based on the available data, no additional benefit of enzalutamide could be established in overall survival.

In the morbidity endpoint category, only some of the available endpoints, i.e., study results, would permit valid inferences to be made. As a result, it was neither possible to establish benefits nor detriments of enzalutamide therapy in general. 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 start of cytotoxic chemotherapy" do not allow any valid conclusions to be drawn on the additional benefit of enzalutamide, in particular due to the fact that 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 enzalutamide treatment was neither positive nor negative.

In the adverse event endpoint category, only specific adverse events were shown to be statistically significant. Both benefits and detriments were established; the extent and clinical significance of these differences, however, are limited, and are not judged to be so significant that they would justify an influence on the overall assessment of the additional benefit.

The overall view of the PROSPER study led the G-BA to conclude on the basis of the criteria in Section 5, paragraph 7 of the AM-NutzenV, taking into account the severity of the disease, that it has not be proven that enzalutamide provides an additional benefit compared to the appropriate comparator therapy in treating adult men with non-metastatic castration-resistant high-risk prostate cancer.

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 enzalutamide 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 PROSPER study available for this assessment are premature due to the limited number of occurrences at the time of the data cut-off. Further findings on overall survival from an interim analysis and the final results from the ongoing study have not yet been published.

In view of the fact that clinical data on overall survival relevant for the benefit assessment of the drug are expected in the future, the G-BA considers it appropriate to limit the period of validity of the resolution until further scientific evidence on the benefit of enzalutamide is available. The time limit will permit the upcoming results from a further interim analysis of the PROSPER study to be promptly incorporated into the benefit assessment of the drug in accordance with Section 35a SGB V.

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

Conditions of the limitation:

In 2020 the ongoing PROSPER study will be releasing an interim analysis for all endpoints after 440 deaths. A new benefit assessment after expiry of the time limit will require these findings to be included in its dossier.

The G-BA is able, in principle, to revise the time limit, if it has been presented with clear justification that it is insufficient or too long.
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 enzalutamide 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 enzalutamide compared to an appropriate comparator (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). If the dossier is not submitted or submitted incompletely, the G-BA may conclude that an additional benefit has not been proven.
The possibility that a benefit assessment for enzalutamide 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 is an assessment of the benefits of the active ingredient enzalutamide in a new therapeutic indication:

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

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 PROSPER study, in which enzalutamide 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 conclusions on 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 cut-offs for the overall survival endpoint are pending.

In the morbidity endpoint category, it has not been proven that treatment with enzalutamide is beneficial or detrimental. However, the uncertainties of the results for the endpoints "metastasis-free survival", "time to onset of cytotoxic chemotherapy" and "state of health" 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.

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

In the adverse event endpoint category, only specific adverse events were shown to be statistically significant. Both benefits and detriments were established; these differences, however, are limited, and it would be invalid to draw on these, as a result, in establishing an overall assessment of additional benefit. In conclusion, the additional benefit of treatment with enzalutamide has not been demonstrated.

<u>Expiry of the resolution</u>

The resolution shall expire on 15 May 2020. The overall survival data from the PROSPER study presented for this assessment are premature. Further findings on overall survival are still pending.

In 2020 the PROSPER study will be releasing an interim analysis for all endpoints. A new benefit assessment after expiry of the time limit will require these findings to be included in its dossier.

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).
This resolution is based on the number of patients specified in the pharmaceutical manufacturer's dossier. The pharmaceutical manufacturer's approach is mathematically plausible, but the number of patients thus deduced is subject to uncertainty. It is generally assumed that the stated number of patients is an underestimate. This is due, in particular, to the fact that in determining the population of patients with prostate cancer, the pharmaceutical manufacturer has employed data on five-year prevalence, which does not include all patients with prostate cancer. From the paper cited by the pharmaceutical manufacturer, it would be possible to infer a ten-year prostrate cancer prevalence, which, given an absolute ten-year survival rate of 59% (57% to 62%), would suggest a higher population.
In determining the target population, the pharmaceutical manufacturer has also employed a number of sources to determine percentages, some of which are associated with further uncertainties, while the suitability of others cannot be conclusively assessed.

2.3 Requirements for quality-assured application

The guidelines in the product information must be observed. The European Medicines Agency (EMA) has published the contents of the technical information on Xtandi® (active ingredient: Enzalutamide) under the following link (last access: 28. Februar 2019):

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

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 technical information and the information listed in the LAUER-TAXE® (last revised: 15. April 2019).

Treatment period:

If no maximum treatment duration is specified in the specialist 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				
Enzalutamide	continuous, 1 x daily	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ Year
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				
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

Usage and consumption:

Designation of the therapy	Dosage	Dose/patient/day of treatment	Consumption based on medication potency/treatment day	No. treatment days/ patient/ year	Annual consumption based on medication potency
Medicinal product to be assessed					
Enzalutamide	160 mg	160 mg	4 × 40 mg	365	1460 × 40 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
Orchiectomy	One-time intervention				
Appropriate comparator:					
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 discounts in accordance with Section 130 and Section 130a SGB V. To calculate the annual costs of treatment, 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 discounts.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Discount Section 130 SGB V	Discount Section 130a SGB V	Costs after deduction of statutory discounts
Medicinal product to be assessed					
Enzalutamide	112 FCT	€ 3,500.09	€ 1.77	€ 0.00	€ 3,498.32
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	€ 555.41	€ 1.77	€ 30.14	€ 523.50
Appropriate comparator					
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	€ 555.41	€ 1.77	€ 30.14	€ 523.50
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. April 2019

<u>Costs for additionally required SHI services:</u>

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed in accordance with the product information or the appropriate comparator, 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.

As there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed in accordance with the product information or the appropriate comparator, no costs were incurred for additionally required SHI

services.

3. Bureaucratic costs

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

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its meeting on 8. August 2017.

On 19. November 2018, the pharmaceutical manufacturer 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 2 VerfO.

In its letter dated 19. November 2018 in conjunction with the G-BA's resolution of 1 August 2011 to commission the IQWiG to assess the benefit of medicinal products containing new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to evaluate the dossier on the active ingredient Enzalutamide.

The IQWiG's evaluation of the dossier was submitted to the G-BA on 27. Februar 2019, and with its publication on 1. März 2019 on the G-BA website, the written statement procedure was initiated. The deadline for submitting written statements was 22. März 2019.

The oral hearing was held on 8. April 2019.

In a letter dated 8. April 2019, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum created by the IQWiG was submitted to the G-BA on 25. April 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 from the IQWiG also participate in the meetings.

The evaluation of the received written statements and the oral hearing were discussed at the meeting of the subcommittee on 7. Mai 2019, and the proposed resolution was approved.

At its meeting on 16. Mai 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Meeting	Date	Subject of consultation
Subcommittee Medicinal products	8. August 2017	Determination of appropriate comparator therapy
Working group Section 35a	2. April 2019	Information on received written statements; preparation of the oral hearing
Subcommittee Medicinal products	8. April 2019	Conduct of the oral hearing Commissioning of the IQWiG with supplementary evaluation of documents

Working group Section 35a	16. April 2019 30. April 2019	Advice on the IQWiG's dossier evaluation and evaluation of the written statement procedure
Subcommittee Medicinal products	7. May 2019	Concluding discussion of the proposed resolution
Plenum	16. May 2019	Adoption of a resolution on the amendment of Appendix XII AM-RL

Berlin, 16. May 2019

Federal Joint Committee
in accordance with Section 91 SGB V
Chair

Prof. Hecken