Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Enzalutamide (new therapeutic indication: prostate cancer, metastatic, hormone-sensitive, combination with androgen deprivation therapy)

of 19 November 2021

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 studies 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 benefits,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient enzalutamide (Xtandi) was listed for the first time on 1 September 2013 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 30 April 2021, Xtandi received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the European Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 27 May 2021, the pharmaceutical company has submitted a dossier in due time, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient enzalutamide with the new therapeutic indication (treatment of adult male with metastatic, hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 September 2021, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of enzalutamide compared with the appropriate comparator therapy could be determined 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, and the addendum to the benefit assessment prepared by 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 Methods1 was not used 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 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 enzalutamide (Xtandi) in accordance with the product information

Xtandi is indicated for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy.

Therapeutic indication of the resolution (resolution from 19.11.2021):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

<u>Adult men with metastatic hormone-sensitive prostate cancer</u>

Appropriate comparator therapy:

- conventional androgen deprivation in combination with docetaxel with or without prednisone or prednisolone (only for patients with remote metastases (M1 stage) and good general condition (0 to 1 according to ECOG / WHO or ≥ 70 % according to Karnofsky index))

or

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

- conventional androgen deprivation in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed, high-risk, metastatic, hormone-sensitive prostate cancer)

or

- conventional androgen deprivation in combination with apalutamide (only for patients with good general condition (0 to 1 according to ECOG / WHO))

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 in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy, for which endpoint studies are available and which has proven its worth in practical application, unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must principally have a marketing authorisation for the therapeutic indication.

2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.

3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant benefit 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 enzalutamide, the active ingredients bicalutamide, cyproterone acetate, flutamide, degarelix, buserelin, goserelin, leuprorelin, triptorelin, abiraterone acetate, apalutamide and docetaxel are approved for the present therapeutic indication.

on 2. Orchiectomy is generally considered a non-medicinal treatment in the present therapeutic indication.

on 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- abiraterone acetate by resolution of 7 June 2018
- apalutamide by resolution of 20 August 2020

on 4. The generally accepted state of medical knowledge was established using a systematic search for guidelines and reviews of clinical studies. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a paragraph 7 SGB V.

Among the approved active ingredients listed under 1.), only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care.

In determining the present appropriate comparator therapy, it is assumed that combination therapy - additional therapy to conventional androgen deprivation therapy - is usually an option for the patients, taking into account any comorbidities and the general condition.

Current guidelines and the scientific-medical societies in the written statement concur in recommending therapy with apalutamide, enzalutamide, or abiraterone acetate or chemotherapy with docetaxel in addition to conventional androgen deprivation therapy (ADT) in patients with metastatic (M1), hormone-sensitive prostate cancer (mHSPC). The background to these recommendations is that, compared with conventional ADT alone, relevant advantages in therapeutic benefit have been shown for these combinations both by combination with docetaxel and with the other therapies mentioned.

In the recommendations, the guidelines take into account that the study populations were defined in different ways, based on metastatic pattern or Gleason score, in the marketing authorisation studies for docetaxel and abiraterone acetate (plus prednisone/prednisolone). In the CHAARTED marketing authorisation study for docetaxel, patients were divided by volume (high and low) with regard to tumour burden. The marketing-authorisation-related LATITUDE study of abiraterone acetate included only patients who were de novo metastatic and had a high-risk profile. The S3 guideline, therefore, classifies patients by high and low volume and high and low risk).

The scientific-medical societies in the written statement follow the categorisation of the guidelines, but note that data on patients with low tumour burden are inconsistent, and chemotherapy may be beneficial regardless of tumour burden.

In the corresponding benefit assessment on abiraterone acetate, an indication of a considerable additional benefit of combination therapy with ADT and prednisone or prednisolone compared to conventional ADT was identified for patients with newly diagnosed high-risk, metastatic prostate cancer (resolution of 07.06.2018). In the benefit assessment of apalutamide in combination with ADT, no additional benefit was identified for patients with remote metastases (M1 stage) and good general condition (0 to 1 according to ECOG / WHO or ≥ 70 % according to Karnofsky index), compared to docetaxel in combination with prednisolone and ADT (resolution of 20.08.2020).

In the context of the present therapeutic indication, conventional androgen deprivation therapy refers to surgical or medicinal castration by therapy with GnRH agonists or GnRH antagonists. Metastatic, hormone-sensitive prostate cancer is a palliative therapy situation. Therefore, maintaining quality of life and symptom control are of particular importance.

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

Change of the appropriate comparator therapy:

Originally, the appropriate comparator therapy was determined as follows:

- conventional androgen deprivation in combination with docetaxel with or without prednisone or prednisolone (only for patients with remote metastases (M1 stage) and good general condition (0 to 1 according to ECOG / WHO or ≥ 70 % according to Karnofsky index))

or

- conventional androgen deprivation in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed, high-risk, metastatic, hormone-sensitive prostate cancer)

With the present determination of the appropriate comparator therapy, conventional androgen deprivation in combination with apalutamide is added as a further, equally appropriate comparator therapy. This takes particular account of the statements submitted by the scientific-medical societies in the present benefit assessment procedure.

This change to the appropriate comparator therapy has no effects on the present assessment of the additional benefit, nor does it require the benefit assessment to be carried out again.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of enzalutamide in combination with androgen deprivation therapy for the treatment of adult men with metastatic hormone-sensitive prostate cancer is assessed as follows:

An additional benefit is not proven.

Justification:

The pharmaceutical company presents a direct comparison with the ENZAMET study in the dossier to demonstrate an additional benefit of enzalutamide in combination with conventional androgen deprivation therapy (ADT), compared to the appropriate comparator therapy. Furthermore, an adjusted indirect comparison according to Bucher et al. was performed by the pharmaceutical company. For this purpose, the randomised controlled trials (RCT) ARCHES and ENZAMET were used on the side of enzalutamide in combination with ADT and the RCT STAMPEDE and CHAARTED on the side of docetaxel in combination with ADT. The bridge comparator was ADT (+ placebo).

ENZAMET study

The ENZAMET study is a multicentre, randomised, open-label study comparing enzalutamide in combination with ADT versus ADT in combination with nonsteroidal anti-androgens (NSAA). In both study arms, concomitant treatment with docetaxel for a maximum of 6 cycles was allowed if this was determined prior to randomisation. Concomitant administration of prednisone or prednisolone was not planned.

A total of 1,125 patients were randomised 1:1 into the study, 563 patients into the intervention arm and 562 patients into the comparator arm. For the direct comparison, the pharmaceutical company draws on one sub-population per treatment arm. In the

enzalutamide + ADT arm, only patients not receiving docetaxel (N=309) were included. In the comparator arm, the pharmaceutical company draws on patients who received docetaxel in addition to NSAA + ADT treatment (N=171). For the indirect comparison of enzalutamide, the pharmaceutical company presents the sub-population of both treatment arms that did not receive concomitant treatment with docetaxel (N = 309 in the intervention arm and N = 313 in the comparator arm).

The primary endpoint is overall survival, and further endpoints are clinical or biochemical progression-free survival (PFS), endpoints on morbidity and health-related quality of life, and adverse events (AEs).

ARCHES study

The ARCHES study is a multicentre, double-blind RCT in a parallel-group design, comparing enzalutamide in combination with ADT versus placebo in combination with ADT. This assessment is based on the final pre-specified data cut-off of 28 May 2021.

The study included 1,150 adult males with metastatic, hormone-sensitive prostate cancer (mHSPC) and a general condition according to ECOG-PS of 0 or 1. Randomisation was in a 1:1 ratio to one of the two study arms, stratified by prior docetaxel therapy (none versus 1-5 cycles versus 6 cycles) and tumour burden (low versus high). In accordance with the approved therapeutic indication, the pharmaceutical company only submits data for the benefit assessment on the sub-population, in which metastasis was confirmed by an independent central review at the start of study. This comprises 93% of the total ARCHES study population (536 patients on enzalutamide and ADT and 531 patients on placebo and ADT).

The intake of enzalutamide was compliant with marketing authorisation. ADT could be performed surgically or medicinally by administration of GnRH analogues. Up to 6 cycles of prior docetaxel therapy were allowed if completed 2 months prior to the start of the study.

The primary endpoint is radiographic progression-free survival. Other patient-relevant endpoints include overall survival, morbidity endpoints, health-related quality of life and AEs.

STAMPEDE study

The STAMPEDE study is a randomised, open-label, multi-arm, multi-stage platform study comparing different systemic active ingredients (12 arms in total) in advanced or metastatic prostate cancer.

The study included adult males with hormone-sensitive prostate cancer and WHO-PS ≤ 2 whose clinical picture met one of the following three criteria:

- newly diagnosed with existing remote metastases or metastases in lymph nodes,
- newly diagnosed with high-risk, locally advanced prostate cancer without remote metastases or lymph node metastases,
- relapsed, locally advanced or metastatic disease, which has already been treated with radiotherapy and/or surgery.

A total of 1,776 patients were included in the study arms C (docetaxel in combination with ADT and prednisolone; intervention arm) and A (ADT; comparator arm) relevant to this assessment, of whom 592 patients were allocated to the intervention arm and 1,184 to the comparator arm.

The STAMPEDE study included patients with remote metastases as well as patients with locally advanced prostate cancer. According to the marketing authorisation of enzalutamide, only the sub-population of patients with hormone-sensitive prostate cancer with remote metastases is relevant for the present assessment. This includes 362 patients in the intervention arm and 724 patients in the comparator arm. The majority of patients in the relevant sub-population have a WHO PS of 0 (intervention arm: 74.6% and comparator arm 72%, respectively). For the remaining patients, a WHO PS of 1 to 2 is given.

In accordance with the requirements in the product information for docetaxel, treatment in the intervention arm was for a maximum of 6 cycles, or until disease progression, unacceptable toxicity, withdrawal of consent, initiation of new cancer therapy, or decision by the physician on therapy discontinuation. ADT could be performed both surgically and medicinally by administration of GnRH analogues. If ADT was performed at start of study, it had to have been in place for at least 14 days but no longer than 3 months. Treatment with ADT in the relevant study arms was continued according to protocol for at least 2 years or until occurrence of the first radiological, clinical or biochemical progression.

The primary endpoint for the study arms of the STAMPEDE study relevant to this assessment is overall survival. Other patient-relevant endpoints include symptomatic skeletal events, other symptomatology, health status, health-related quality of life and AE.

CHAARTED study

The CHAARTED study is an open-label, randomised controlled trial, comparing treatment with docetaxel in combination with ADT versus ADT in patients with metastatic prostate cancer. In both study arms, combined administration with NSAA in the sense of maximal androgen blockade (MAB) was possible. Adult patients with pathologically confirmed prostate cancer or a diagnosis of prostate cancer via an elevated prostate-specific antigen (PSA) level, radiological evidence of remote metastases, and an ECOG-PS ≤ 2 were included. Patients receiving ADT for the treatment of metastatic prostate cancer were included if therapy was started 120 days or less prior to randomisation and there had been no evidence of disease progression since.

A total of 790 patients were randomised into the study in a 1:1 ratio. In the intervention arm of the study, treatment was with docetaxel according to the German authorisation status with up to 6 cycles and concomitant therapy with dexamethasone. In both study arms, ADT could be performed surgically or medicinally by administration of GnRH analogues until the development of resistance. In case of non-response to hormone therapy, patients in the comparator arm were able to switch to docetaxel therapy.

The primary endpoint was defined as overall survival. Other endpoints included time to clinical progression, time to castration-resistant prostate cancer, morbidity, as well as change in health-related quality of life and AE.

Assessment of the suitability of the direct and indirect comparisons

The direct comparison with the ENZAMET study was not used in IQWIG's dossier assessment because the appropriate comparator therapy was not implemented. The pharmaceutical company deviates from the appropriate therapy defined by the G-BA by considering the combination of ADT with NSAA as being included in the appropriate comparator therapy. For indirect comparison with this study, the bridge comparator ADT alone versus ADT + NSAA is not considered to be similar enough. The study is therefore not included in the present assessment.

The CHAARTED study was also not used in IQWIG's dossier assessment because the appropriate comparator therapy was not implemented (combination of ADT with NSAA) on the one hand, and the bridge comparator ADT alone versus ADT + NSAA is not similar enough on the other. The study is therefore not included in the present assessment.

For the indirect comparison with the ARCHES und STAMPEDE studies, there are differences in study and patient characteristics. In terms of study design, the ARCHES study is a double-blinded study, while the STAMPEDE study is unblinded. Furthermore, the studies differ in terms of recruitment periods, thus also in the potential availability of concomitant and subsequent therapies. The STAMPEDE study was initiated as early as October 2005, while the ARCHES study was initiated in 2016, which meant that it was only during the course of the STAMPEDE study that denosumab became available as a concomitant medication and enzalutamide or abiraterone acetate as subsequent therapies. Another difference arises from the pretreatment with ADT allowed in the ARCHES study, which more than 90% of the participants received. In contrast to the STAMPEDE study, pretreatment with docetaxel was also allowed in the ARCHES study.

In the overall assessment, however, the described differences do not lead to a fundamental questioning of the similarity of the studies.

For the present assessment, the adjusted indirect comparison, according to Bucher et al., based on the ARCHES and STAMPEDE studies, was used. The ARCHES study forms the intervention side with enzalutamide + ADT, while the STAMPEDE study forms the comparison side with docetaxel + prednisolone + ADT. Placebo + ADT or ADT acts as the bridging comparator.

ARCHES study data submitted in the written statement

In its written submission, the pharmaceutical company submits new evaluations of the final data cut-off of 28 May 2021 for the ARCHES study. In Addendum A21-132, IQWiG assessed these data for the indirect comparison for overall survival, symptomatic skeletal events, serious adverse events (SAE), and severe adverse events (AE). These data are used for the present benefit assessment.

Extent and probability of the additional benefit

Mortality

The requirement for the certainty of results to conduct an adjusted indirect comparison is not met since the results of the STAMPEDE study have a low risk of bias while those of the ARCHES study a high risk of bias. No statement with sufficient certainty of results can be deduced on the additional benefit.

An additional benefit is not proven.

Morbidity

Symptomatology

Symptomatology was assessed in the ARCHES and STAMPEDE studies, partly using different measurement instruments. In the ARCHES study, the BPI-SF and the EORTC QLQ-PR25 were used for the assessment. However, the EORTC QLQ-PR25 can only be evaluated in combination with the core questionnaire EORTC QLQ-C30 and is therefore not used here. In

the STAMPEDE study, data on symptomatology were collected using the EORTC QLQ-C30 and EORTC QLQ-PR25 measurement instruments.

Thus, there are no usable data for an indirect comparison. An additional benefit is not proven.

Symptomatic skeletal events

For the endpoint on symptomatic skeletal events, there are no usable data for an adjusted indirect comparison.

This is justified by the insufficient similarity of the endpoints in the ARCHES and STAMPEDE studies. Thus, there are significantly different rates of patients with a skeletal event at all time points in the comparator arms of the studies. Although medicinal prevention of skeletal events was allowed, in principle, in both studies, no comprehensive information is available on the number of patients and which active ingredient was actually used.

Health status

For the endpoint on health status, no data are available for an indirect comparison, as this endpoint was not collected in the STAMPEDE study. An additional benefit is not proven.

In summary, in the category of morbidity, an additional benefit of enzalutamide + ADT is not proven.

Quality of life

In the ARCHES study, data on health-related quality of life were collected using the FACT-P and EORTC QLQ-PR25 measurement instruments. However, the EORTC QLQ-PR25 can only be evaluated in combination with the core questionnaire EORTC QLQ-C30. In the STAMPEDE study, the assessment was conducted using the EORTC QLQ-C30 and the EORTC QLQ-PR25. Due to the different measurement instruments in the studies, it is not possible to perform an indirect comparison.

In the quality of life category, an additional benefit of enzalutamide + ADT is therefore not proven.

Side effects

Adverse events (AEs) in total

Adverse events occurred in almost all participants of the STAMPEDE study. In the ARCHES study, an AE was observed in 86% of the patients. The results were only presented additionally.

Serious adverse events (SAE)

For the SAE endpoint, the adjusted indirect comparison showed a statistically significant difference for the advantage of enzalutamide + ADT over docetaxel + prednisolone + ADT. While both studies have a high endpoint-specific risk of bias, this advantage in SAEs is not expected to be entirely challenged by the potential risk of biases, given the magnitude of this effect. However, due to the different durations of observation in the comparison and intervention arms of the STAMPEDE study, this advantage can only be derived for the period of the first 6 to 7 months after the start of treatment with an effect estimate that can be interpreted with sufficient certainty. Statements beyond this period cannot be made.

Severe AEs (CTCAE grade 3 or 4)

The requirement for the certainty of results for conducting an adjusted indirect comparison is not met due to the high endpoint-specific risk of bias in the ARCHES and STAMPEDE studies. No statement on relevant differences can be derived with sufficient certainty of results.

An additional benefit is not proven.

Discontinuation due to AE

For the endpoint on discontinuation due to AEs, no data are available for an indirect comparison, as this endpoint was not collected in the STAMPEDE study. An additional benefit is not proven for this endpoint.

In the overall assessment, enzalutamide + ADT showed an advantage in terms of side effects in serious adverse events (SAE). However, due to the different durations of observation in the arms of the STAMPEDE study, this advantage can only be derived for the period of the first 6 to 7 months after the start of treatment with an effect estimate that can be interpreted with sufficient certainty. Statements beyond this period cannot be made. Regarding the severe AEs, no statement on relevant differences can be made with sufficient certainty of results. No data from the indirect comparison are available for the endpoint on discontinuation due to AE. For these reasons, no overall additional benefit can be identified for enzalutamide + ADT with the required certainty in the category of side effects.

Overall assessment / conclusion

For the assessment of the additional benefit of enzalutamide in combination with an androgen deprivation therapy for the treatment of adult men with metastatic hormone-sensitive prostate cancer, results on mortality, morbidity and side effects compared with the appropriate comparator therapy are available.

The present assessment is based on an adjusted indirect comparison of the ARCHES (enzalutamide + ADT versus placebo + ADT), and STAMPEDE (docetaxel + prednisolone + ADT versus ADT) studies via the bridge comparator placebo + ADT and ADT, respectively.

The final data of the ARCHES study submitted during the written statement procedure were assessed by IQWiG in the addendum and used here.

For the endpoint on overall survival, the requirement for the certainty of results to conduct an adjusted indirect comparison is not met. An additional benefit with regard to overall survival is therefore not proven.

There are no usable data from the adjusted indirect comparison for the categories of morbidity and health-related quality of life. Symptomatology and health-related quality of life were assessed, partly with different measurement instruments. For the endpoint on symptomatic skeletal events, sufficient endpoint-related similarity between the two studies is not assumed.

In the overall assessment, enzalutamide + ADT showed an advantage in terms of side effects in serious adverse events. However, due to the different durations of observation in the arms of the STAMPEDE study, this advantage can only be derived for the period of the first 6 to 7 months after the start of treatment with an effect estimate that can be interpreted with sufficient certainty. Statements beyond this period cannot be made. Regarding the severe AEs, no statement on relevant differences can be made with sufficient certainty of results. No data from the indirect comparison are available for the endpoint on discontinuation due to AE. For

these reasons, no overall additional benefit can be identified for enzalutamide + ADT with the required certainty in the category of side effects.

In the overall assessment, the G-BA thus concludes that an additional benefit of enzalutamide + ADT, compared to docetaxel + prednisolone + ADT in the treatment of metastatic, hormone-sensitive prostate cancer is not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient enzalutamide.

Enzalutamide is used to treat adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy.

The G-BA defined conventional androgen deprivation in combination with apalutamide (only for patients with good general condition (0 to 1 according to ECOG / WHO)) *or* in combination with docetaxel with or without predniso(lo)ne (only for patients with remote metastases and good general condition (0 to 1 according to ECOG / WHO or ≥ 70% according to Karnofsky index) *or* in combination with abiraterone acetate and predniso(lo)ne (only for patients with newly diagnosed high-risk, metastatic HSPC) as appropriate comparator therapy.

For the proof of an additional benefit, the pharmaceutical company submits a direct comparison with the ENZAMET study and an adjusted indirect comparison according to Bucher et al. with the ARCHES and ENZAMET as well as STAMPEDE and CHAARTED RCTs.

The direct comparison with the ENZAMET study is not used because the appropriate comparator therapy was not implemented. The ENZAMET and CHAATRED studies are not included for the indirect comparison as the bridge comparator is not considered to be similar enough. The adjusted indirect comparison with the ARCHES and STAMPEDE studies is used.

The final data of the ARCHES study submitted during the written statement procedure were assessed by IQWiG in the addendum and used here.

No additional benefit is determined for overall survival as the requirements for certainty of results for conducting an adjusted indirect comparison are not met. An additional benefit is not proven.

There are no (usable) data from the adjusted indirect comparison for the categories of morbidity and health-related quality of life.

Enzalutamide + ADT showed an advantage in terms of side effects in serious adverse events (SAE). However, due to the different durations of observation in the arms of the STAMPEDE study, this advantage can only be derived for the period of the first 6 to 7 months after the start of treatment with an effect estimate that can be interpreted with sufficient certainty. Statements beyond this period cannot be made. Regarding the severe AEs, no statement on relevant differences can be made with sufficient certainty of results. No data from the indirect comparison are available for the endpoint on discontinuation due to AE. For these reasons, no overall additional benefit can be identified for enzalutamide + ADT with the required certainty in terms of side effects.

In the overall assessment, the G-BA concludes that an additional benefit of enzalutamide + ADT, compared to docetaxel + prednisolone + ADT in the treatment of mHSPC is not proven.

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

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

The G-BA bases its resolution on the information from the dossier of the pharmaceutical company. Overall, it is assumed that this is an underestimate. In its derivation, the pharmaceutical company adds the percentage of newly diagnosed patients with remote metastases to the percentage of patients, who were diagnosed at an earlier stage and newly develop remote metastases in the year under review and are not castration-resistant at the same time. This leaves out patients from previous years with an mHSPC who have not developed resistance to ADT and are eligible for therapy with enzalutamide. Furthermore, the data used to determine the mentioned percentage are based on data in which the assessment of metastasis occurred only 6 weeks after the start of ADT. This neglects patients who only developed metastasis after this period following ADT.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Xtandi (active ingredient: enzalutamide) at the following publicly accessible link (last access: 19 August 2021):

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

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

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 November 2021).

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 patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Enzalutamide	continuously 1 x daily	365	1	365
Androgen deprivation therapy				
Degarelix	continuously 1 x month	12	1	12
Buserelin	continuously every 3 months	4	1	4
Goserelin	continuously every 3 months	4	1	4
Leuprorelin	continuously every 3 months	4	1	4
Triptorelin	continuously every 6 months	2	1	2
Orchiectomy	once		3.8 (average length of stay)[2]	-
Appropriate comparator therapy				
Androgen deprivation therapy				
Degarelix	continuously 1 x month	12	1	12
Buserelin	continuously every 3 months	4	1	4
Goserelin	continuously every 3 months	4	1	4
Leuprorelin	continuously every 3 months	4	1	4
Triptorelin	continuously every 6 months	2	1	2
Orchiectomy	once		3.8 (average length of stay)[2]	-
Androgen deprivation therapy (see above) in combination with apalutamide				
Apalutamide	continuously 1 x daily	365	1	365
Androgen deprivation therapy (see above) in combination with docetaxel and, if applicable, prednis(ol)one				

[2] 2021 Flat Case Fee Catalogue and Nursing Revenue Catalogue, https://www.g-drg.de/aG-DRG-System_2021/Fallpauschalen-Katalog/Fallpauschalen-Katalog_2021, p. 53, accessed on 12.10.2021.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Docetaxel	1 x every 21 days	6	1	6
if applicable, prednisone	2 x daily	6	21	126
if applicable, prednisolone	2 x daily	6	21	126
Androgen deprivation therapy (see above) in combination with abiraterone acetate and prednis(ol)one				
Abiraterone acetate	continuously, 1 x daily	365	1	365
Prednisone	continuously 1 x daily	365	1	365
Prednisolone	continuously 1 x daily	365	1	365

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

For the presentation of the costs, one year is assumed for all medicinal products. This does not take into account the fact that treatment may be discontinued earlier due to non-response or intolerance. The discontinuation criteria according to the product information of the individual active ingredients must be taken into account when using the medicinal products.

The (daily) doses recommended in the product information or in the labelled publications were used as the basis for calculation.

The average body measurements of adult males were applied for dosages depending on body weight or body surface area (average body height: 1.79 m; average body weight: 85 kg).[3] This results in a body surface area of 2.04 m² (calculated according to Du Bois 1916)[4].

[3] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

[4] Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known, Nutrition. 1989 Sep-Oct;5(5):303-11; discussion 312-3. https://www.ncbi.nlm.nih.gov/pubmed/2520314.

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					
Enzalutamide	160 mg	160 mg	4 x 40 mg	365	1,460 x 40 mg
Androgen deprivation therapy					
Degarelix	80 mg	80 mg	1 x 80 mg	12	12 x 80 mg
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4	4 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2	2 x 22.5 mg
Orchiectomy	One-off intervention				
Appropriate comparator therapy					
Androgen deprivation therapy					
Degarelix	80 mg	80 mg	1 x 80 mg	12	12 x 80 mg
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4	4 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2	2 x 22.5 mg
Orchiectomy	One-off intervention				
Androgen deprivation therapy (see above) in combination with apalutamide					
Apalutamide	240 mg	240 mg	4 x 60 mg	365	1,460 x 60 mg
Androgen deprivation therapy (see above) in combination with docetaxel and, if applicable, prednis(ol)one					
Docetaxel	75 mg/m^2 body surface area	153 mg	1 x 160 mg	6	6 x 160 mg
if applicable, prednisone	5 mg	10 mg	2 x 5 mg	126	252 x 5 mg
if applicable, prednisolone	5 mg	10 mg	2 x 5 mg	126	252 x 5 mg
Androgen deprivation therapy (see above) in combination with abiraterone acetate and prednis(ol)one					
Abiraterone acetate	1,000 mg	1,000 mg	2 x 500 mg	365	730 x 500 mg
Prednisone	5 mg	5 mg	1 x 5 mg	365	365 x 5 mg
Prednisolone	5 mg	5 mg	1 x 5 mg	365	365 x 5 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Enzalutamide	112 FCT	€ 3,455.99	€ 1.77	€ 0.00	€ 3,454.22
Androgen deprivation therapy					
Degarelix	3 PSI	€ 574.16	€ 1.77	€ 31.18	€ 541.21
Buserelin	2 PS	€ 1,027.87	€ 1.77	€ 56.30	€ 969.80
Goserelin	2 IMP	€ 1,013.29	€ 1.77	€ 55.49	€ 956.03
Leuprorelin	2 IMP	€ 730.51	€ 1.77	€ 86.93	€ 641.81
Triptorelin	1 DSS	€ 944.17	€ 1.77	€ 51.66	€ 890.74
Orchiectomy					€ 3,852.53[5]
Appropriate comparator therapy					
Androgen deprivation therapy					
Degarelix	3 PSI	€ 574.16	€ 1.77	€ 31.18	€ 541.21
Buserelin	2 PS	€ 1,027.87	€ 1.77	€ 56.30	€ 969.80
Goserelin	2 IMP	€ 1,013.29	€ 1.77	€ 55.49	€ 956.03
Leuprorelin	2 IMP	€ 730.51	€ 1.77	€ 86.93	€ 641.81
Triptorelin	1 DSS	€ 944.17	€ 1.77	€ 51.66	€ 890.74
Orchiectomy					€ 3,852.53[5]
Androgen deprivation therapy (see above) in combination with apalutamide					
Apalutamide	112 FCT	€ 2,831.15	€ 1.77	€ 0.00	€ 2,829.38
Androgen deprivation therapy (see above) in combination with docetaxel and, if applicable, prednis(ol)one					
Docetaxel	1 CIS	€ 1,397.36	€ 1.77	€ 175.44	€ 1,220.15
if applicable, prednisone[6]	100 TAB	€ 16.47	€ 1.77	€ 0.43	€ 14.27

[5] Surgery and procedure code 5-622.3, diagnosis code C61 (ICD-10-GM 2021), flat case fee M04B (G-DRG 2021). Calculation with the grouping engine GetDRG-Grouper (2021, v20.2.0.0) of the Gesellschaft für den Einsatz offener Systeme mbH (GEOS), provided by the DRG-Research Group. The fee includes the basic fee of € 3,339.45 plus a nursing fee of € 513.08 for a stay of 4 days. The mean length of stay of 3.8 days was rounded to whole days for calculation purposes.
[6] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
if applicable, prednisolone[6]	100 TAB	€ 15.16	€ 1.77	€ 0.33	€ 13.06
Androgen deprivation therapy (see above) in combination with abiraterone acetate and prednis(ol)one					
Abiraterone acetate	56 FCT	€ 3,518.47	€ 1.77	€ 0.00	€ 3,516.70
Prednisone[6]	100 TAB	€ 16.47	€ 1.77	€ 0.43	€ 14.27
Prednisolone[6]	100 TAB	€ 15.16	€ 1.77	€ 0.33	€ 13.06
Abbreviations: PS: prefilled syringe; FCT: film-coated tablets; CIS: concentrate for the preparation of an infusion solution; IMP: implant; PSI: powder and solvent for solution for injection; TAB: tablets; DSS: dry substance with solvent for the preparation of prolonged-release suspension for injection					

LAUER-TAXE® last revised: 1 November 2021

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

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

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1 October 2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but instead follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active

ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 27 October 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 27 May 2021, the pharmaceutical company submitted a dossier for the benefit assessment of enzalutamide to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 31 May 2021, in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient enzalutamide.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 August 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 September 2021. The deadline for submitting written statements was 22 September 2021.

The oral hearing was held on 11 October 2021.

By letter dated 12 October 2021, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addenda prepared by IQWiG was submitted to the G-BA on 29 October 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 9 November 2021, and the proposed resolution was approved.

At its session on 19 November 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	27 October 2020	Determination of the appropriate comparator therapy
Working group Section 35a	6 October 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	11 October 2021 12 October 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	20 October 2021 3 November 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	9 November 2021	Concluding discussion of the draft resolution
Plenum	19 November 2021	Adoption of the resolution on the amendment of Annex XII AM-RL (Pharmaceuticals Directive)

Berlin, 19 November 2021

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

Prof. Hecken