Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Apalutamide (New Therapeutic Indication: Metastatic Hormone-sensitive Prostate Cancer (mHSPC))

of 20 August 2020

Contents

1. Legal basis

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

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

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

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

2. Key points of the resolution

The active ingredient apalutamide (Erleada®) was listed for the first time on 1 February 2019 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices. On 29 January 2020, apalutamide (Erleada®) received marketing authorisation for a new therapeutic indication:

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

On 24 February 2020, the pharmaceutical company submitted a dossier 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 apalutamide with the new therapeutic indication in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 2 June 2020, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of apalutamide compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has assessed the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of apalutamide.

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

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

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

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

2.1.2 Appropriate comparator therapy

Adult men with metastatic hormone-sensitive prostate cancer (mHSPC)

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

  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)

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.

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

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

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

On 1. Medicinal products with the following active ingredients are approved for the present therapeutic indication:

Bicalutamide, flutamide, cyproterone acetate, abiraterone acetate, degarelix, buserelin, goserelin, leuprorelin, triptorelin, and docetaxel

On 2. As a non-medicinal treatment option, an orchiectomy in addition to the use of GnRH agonists or GnRH antagonists represents a possibility for implementing conventional androgen deprivation (ADT).

Other non-medicinal treatment options are not considered. The implementation of radiotherapy as a patient-individual palliative therapy option remains unaffected.

On 3. A resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V has been passed on abiraterone acetate (resolution of 7 June 2018).

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

In accordance with the S3 guideline[2], patients in good general condition (ECOG 0-1) with metastatic (M1) hormone-sensitive prostate carcinoma were to be recommended chemotherapy with docetaxel or supplementary anti-hormonal therapy with abiraterone acetate in addition to conventional ADT. In the corresponding benefit assessment on abiraterone acetate, the resolution of 7 June 2018 for the combination therapy with ADT and prednisone or prednisolone for patients with newly diagnosed high-risk metastatic prostate cancer found an indication of a considerable additional benefit compared with conventional ADT.

Only for those patients who are ineligible for combination treatment is a single conventional ADT recommended; this can be performed either surgically by orchiectomy or medicinally with GnRH agonists or antagonists. For the adult patients with mHSPC covered by the present therapeutic indication, in line with the guideline recommendations, the G-BA assumes that with regard to possible co-morbidities and the general condition, a combination therapy in addition to conventional ADT is regularly considered and that the patients have distant metastases (M1).

In the overall view, the conventional androgen deprivation in combination with docetaxel with or without prednisone or prednisolone (only for patients with distant metastases (M1 stage) and good general condition (according to ECOG/WHO 0 to 1 or Karnofsky Index ≥ 70%) 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) has therefore been determined to be an appropriate comparator therapy.

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

Change of the appropriate comparator therapy

[2] Interdisciplinary guideline of quality S3 for the early detection, diagnosis, and therapy of the various stages of prostate carcinoma; long version 5.1. AWMF register number 043-022OL.

The appropriate comparator therapy was originally determined as follows:

- Conventional androgen deprivation in combination with docetaxel and prednisone or prednisolone (only for patients with distant metastases (M1 stage) and good general condition (according to ECOG/WHO 0 to 1 or Karnofsky Index ≥ 70%)

  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)".

The adjustment of the appropriate comparator therapy with regard to an optional use of prednisone or prednisolone within the framework of the therapy option for docetaxel takes into account the marketing authorisation of docetaxel for this therapeutic indication, which had been granted in the meantime.

In the dossier, the pharmaceutical company submitted the CHAARTED study as a further study for an indirect comparison. However, the IQWiG did not use this study in the dossier assessment because of the lack of concomitant administration of prednisone or prednisolone, the treatment did not correspond to the originally determined appropriate comparator therapy. Against the background of the adjustment of the appropriate comparator therapy, the IQWiG was commissioned to assess the influence of the CHAARTED study on the results of the dossier assessment. The addendum of the IQWiG shows that inclusion of the CHAARTED study does not affect the dossier assessment.

This change in the appropriate comparator therapy has no effect on this benefit assessment nor does it require a repeated implementation of this.

2.1.3 Extent and probability of the additional benefit

Adult men with metastatic hormone-sensitive prostate cancer (mHSPC)

In summary, the additional benefit of apalutamide in combination with ADT (for patients with distant metastases (M1 stage) and good general condition (according to ECOG/WHO 0 to 1 or Karnofsky Index ≥ 70%)) is assessed as follows:

An additional benefit is not proven.

Justification:

In the absence of a direct comparative study to prove an additional benefit of apalutamide in combination with ADT compared with the appropriate comparator therapy, the pharmaceutical company submitted an adjusted indirect comparison according to Bucher in the dossier. For this, the pharmaceutical company uses the randomised controlled trial (RCT) TITAN on the side of apalutamide in combination with ADT and the RCT STAMPEDE, GETUG, and CHAARTED on the side of docetaxel in combination with ADT, whereby ADT (+ placebo) was the bridge comparator.

TITAN study

The TITAN study is a double-blind, randomised Phase III study comparing apalutamide in combination with ADT with treatment with ADT and placebo. The study included adult men with an mHSPC and ECOG-PS of 0 or 1 with metastases in the form of at least one proven bone lesion. The patients included had to have either undergone surgical castration or started drug-induced ADT using GnRH analogues (GnRH: gonadotropin-releasing hormone) within a period of 14 days to three months prior to randomisation. Pre-treatment with up to six cycles of docetaxel was allowed.

The 1052 patients were randomised at a ratio of 1:1 and stratified by Gleason score (< 7 vs ≥ 7), geographic region (North America and Europe vs all other countries), and pre-treatment with docetaxel (yes vs no).

Treatment with apalutamide was in accordance with the German authorisation status. Patients were treated until disease progression or unacceptable toxicity and were then able to switch to follow-up therapy. At the data cut-off of 23 November 2018, 16.6% of patients in the intervention arm (apalutamide + ADT) and 36.1% in the comparator arm (placebo + ADT) had already received systemic follow-up therapy, mainly in the form of hormone therapy.

Co-primary endpoints of the study are overall survival and radiographic progression-free survival. Other patient-relevant endpoints include symptomatic local progression (urethral or bladder outlet obstruction), pain, fatigue, skeletal events, health-related quality of life, health status, and adverse events (AE).

The TITAN study was started in 2015 and is still ongoing After the interim analysis of the present data cut-off, the blinding was removed and a change in treatment from the comparator arm to apalutamide in combination with ADT was allowed.

GETUG study

The GETUG study is an open-label, randomised controlled study comparing docetaxel in combination with ADT with ADT in patients with metastatic prostate cancer. Included were adult patients with histologically confirmed prostate carcinoma and an ECOG-PS ≤ 2 or Karnofsky Index ≥ 70% for whom radiological evidence of distant metastases was also available. Patients were not allowed to start ADT for more than two months before inclusion in the study.

A total of 385 patients were randomised into the study at a ratio of 1:1. In the intervention arm of the study, docetaxel in combination with ADT and dexamethasone was used as concomitant treatment for a maximum of nine cycles. The study patients received eight cycles (median) of docetaxel. In both the intervention arm and the control arm, ADT was performed surgically or by means of GnRH agonists (alone or in combination with non-steroidal antiandrogens) until the development of a resistance.

The primary endpoint was defined as overall survival. Other endpoints were clinical or biochemical progression-free survival (PFS), morbidity, changes in health-related quality of life, and AE.

The study patients received eight cycles (median) of docetaxel. This number of therapy cycles with docetaxel is not compliant with marketing authorisation. In accordance with requirements in the product information, docetaxel should be administered to patients with mHSPC for a maximum of six cycles.

Overall, the therapy used in the intervention arm of the GETUG study does not adequately reflect the defined appropriate comparator therapy. The GETUG study is therefore not included in the present assessment.

CHAARTED study

The CHAARTED study is an open, randomised controlled study comparing the treatment of docetaxel in combination with ADT with ADT in patients with metastatic prostate cancer. Included were adult patients with pathologically confirmed prostate carcinoma or a diagnosis of prostate carcinoma via elevated PSA (prostate-specific antigen) levels, radiological evidence of distant metastases, and an ECOG-PS ≤ 2. Patients who received ADT for the treatment of metastatic prostate cancer were included if therapy was initiated no more than 120 days before randomisation and no signs of disease progression had been seen since then.

A total of 790 patients were randomised into the study at a ratio of 1:1. In the intervention arm of the study, treatment with docetaxel was carried out according to the German authorisation status with up to six cycles and a concomitant therapy with dexamethasone. In both study arms, ADT was performed either surgically or medically through the administration of GnRH analogues until resistance developed. Patients in the comparator arm who did not respond to hormone therapy 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, and morbidity as well as changes in health-related quality of life and AE.

The CHAARTED study was not included in the dossier assessment of the IQWiG because concomitant administration of prednisone or prednisolone was not planned and therefore did not meet the requirements of the originally determined appropriate comparator therapy.

Against the background of the adjustment of the appropriate comparator therapy, the IQWiG was commissioned to assess the influence of the CHAARTED study on the results of the dossier assessment under the assumption that the indirect comparison is similar.

From the CHAARTED study, potentially suitable results on mortality and health-related quality of life are available for the adjusted indirect comparison. With regard to overall survival, the CHAARTED study shows no statistically significant difference based on an adjusted indirect comparison of apalutamide + ADT compared with docetaxel + ADT. This is in line with the result of the dossier assessment.

For the endpoint quality of life, data are available from the CHAARTED study; as in the TITAN study, these were surveyed using the FACT-P. However, the risk of bias is considered high because of the lack of blinding. Thus, an effect estimate for the endpoint would not be sufficiently reliable to be considered in an adjusted indirect comparison.

With regard to the side effects category, no data suitable for indirect comparison are available from the CHAARTED study.

Overall, the inclusion of the CHAARTED study has no influence on the results of the benefit assessment.

The CHAARTED study is not included in the present assessment.

STAMPEDE study

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

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

- newly diagnosed with existing distant metastases or metastases in lymph nodes
- newly diagnosed with high-risk locally advanced prostate cancer without distant metastases or metastases in lymph nodes
- relapsed locally advanced or metastatic disease that has already been pretreated with radiotherapy and/or surgery

Study arms C (docetaxel in combination with ADT and prednisolone; intervention arm) and A (ADT; reference arm), which are relevant for the present assessment, included a total of 1776 patients (592 in the intervention arm and 1184 in the reference arm).

According to the requirements in the product information for docetaxel, treatment in the intervention arm was carried out for a maximum of six cycles or until disease progression, unacceptable toxicity, withdrawal of consent, start of a new cancer therapy, or if the doctor decide for therapy discontinuation. ADT could be performed both surgically and medically through the administration of GnRH analogues. If ADT was already carried out at the start of study, it had to have been lasted for at least 14 days but no more than three months. Treatment with ADT in the relevant study arms was continued according to protocol for at least two years or until the first radiological, clinical or biochemical progression occurred.

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

The STAMPEDE study, which is still ongoing, was started in 2005. Patient recruitment for the individual study arms took place over different periods of time. Patients were recruited for the intervention arm between October 2005 and March 2013. For the present data cut-off of 13 July 2018, the evaluation for the comparator arm is based exclusively on patients recruited during this period.

On the relevant sub-population of the STAMPEDE study

The STAMPEDE study included both patients with distant metastases and patients with locally advanced prostate cancer. In accordance with the marketing authorisation of apalutamide, only the sub-population of patients with hormone-sensitive prostate cancer with distant metastases is relevant for the present assessment.

A sub-population of the STAMPEDE study, which includes only patients with distant metastases, was evaluated by the pharmaceutical company. This includes 362 patients in the intervention arm and 724 patients in the comparator arm. In total, this sub-population comprises 61% of the total population included in the study arms.

The majority of patients in this sub-population have a WHO-PS of 0 (intervention arm: 74.6% or comparative arm 72%). For the remaining patients, a WHO-PS of 1 to 2 is given.

However, overall, this sub-population of the STAMPEDE study is considered a sufficient representation of the target population.

On the similarity of TITAN and STAMPEDE studies in the indirect comparison

There are differences between the studies used for the present indirect comparison in terms of recruitment periods and thus also in the potential availability of concomitant and follow-up therapies. Recruitment of study participants in the STAMPEDE study began in October 2005 (TITAN 2015 study), whereby only in the course of the STAMPEDE study did denosumab (as a concomitant medication) and enzalutamide or abiraterone (as follow-up therapies) become available.

Another difference results from the pre-treatment of patients with docetaxel, which was allowed in the TITAN study: but not the STAMPEDE study. This applies to 11% of the patients in the TITAN study.

With regard to the comparability of the bridge comparator, there are differences in that in the TITAN study, patients had to have started their treatment with ADT or GnRH agonists before randomisation. In the STAMPEDE study, ADT was started after randomisation.

In terms of study design, the TITAN study is a double-blind study and the STAMPEDE study is an unblinded study.

Despite the differences between the TITAN and STAMPEDE studies, it is not generally assumed that the similarity assumption must be rejected for the indirect comparison.

The present assessment is therefore based on the adjusted indirect comparison according to Bucher on the basis of the TITAN and STAMPEDE studies. The intervention side is the TITAN study with apalutamide in combination with ADT, and the comparator side is the relevant sub-population of the STAMPEDE study with docetaxel in combination with ADT and prednisolone. The bridge comparator is ADT or placebo + ADT.

Extent and probability of the additional benefit

Mortality

Up to the data cut-off of 23 November 2018, 83 patients (approx. 16%) in the intervention arm and 117 patients in the comparator arm (approx. 22%) of the TITAN study died. The median survival time was not yet achieved in either study arm of the TITAN study.

In the relevant sub-population of the STAMPEDE study, 225 patients (approx. 62%) in the intervention arm and 494 patients (approx. 68%) in the comparator arm had died by the data cut-off of 13 July 2018. The median survival times are 59.1 and 43.1 months, respectively.

In the adjusted indirect comparison, there is no statistically significant difference between apalutamide in combination with ADT and docetaxel in combination with ADT and prednisolone. An additional benefit of apalutamide in combination with ADT is therefore not proven in the mortality category.

On radiological progression-free survival (rPFS) as a surrogate for overall survival

The pharmaceutical company also submitted analyses to validate the rPFS endpoint as a surrogate for overall survival in the dossier. For this purpose, the pharmaceutical company initially calculates two surrogate threshold effect (STE) limits based on a study pool of 16 and 15 RCT, respectively. However, for none of the indirect comparisons (TITAN vs STAMPEDE, TITAN vs GETUG, and CHAARTED and TITAN vs GETUG, CHAARTED, and STAMPEDE) submitted by the pharmaceutical company in the dossier is the respective 95% confidence interval for rPFS completely below the calculated STE limits. The analyses presented therefore do not provide sufficient evidence that the rPFS is a valid surrogate endpoint for overall survival in the present indication.

Morbidity

Time until the 1st skeletal event

In the comparator arms of the two studies, there are clearly different rates of patients with skeletal events at all points in time. For example, when considering the timing of 24 months, approx. 15% of the patients in the comparative arm of the TITAN study and approx. 38% of the patients in the comparative arm of the STAMPEDE study experienced a skeletal event. Although medical prophylaxis of skeletal events was generally allowed in both studies, no comprehensive data are available on the number of patients with appropriate prophylaxis and on the active ingredients used for prophylaxis.

Overall, it is therefore not assumed that the two studies are sufficiently similar with regard to the endpoint. As a result, there are no data for the endpoint skeletal events that can be used for an adjusted indirect comparison.

An additional benefit of apalutamide in combination with ADT is therefore not proven in the morbidity category.

Quality of life

In the TITAN study, data on health-related quality of life were collected using the measuring instrument FACT-P. In the STAMPEDE study, the survey was conducted using the EORTC QLQ-C30. Because of the different measuring instruments used in the studies, an indirect comparison is not possible.

An additional benefit of apalutamide in combination with ADT is therefore not proven in the quality of life category.

Side effects

Adverse events (AE) in total

Nearly every patient in the intervention and comparator arms of the TITAN and STAMPEDE studies experienced an adverse event. The study results for the endpoint “total adverse events” are presented additionally.

Serious AE and severe AE (CTCAE grade ≥ 3).

On the observation and bias of the endpoints SAE and severe AE (CTCAE grade ≥ 3)

In the TITAN study, SAE and severe AE (CTCAE grade ≥ 3) were monitored for up to 30 days after discontinuation of the study medication. In the course of the study, 34% of patients in the intervention arm and 54% of patients in the comparator arm discontinued therapy. This results in a high risk of bias for the results for both endpoints in the TITAN study because of possibly high proportions of patients with incomplete observation that differ between the therapy arms.

In the STAMPEDE study, there are clearly different observation periods between the treatment arms for the endpoints SAE and severe AE (CTCAE grade ≥ 3). Patients in the intervention arm of the STAMPEDE study were followed up with docetaxel for up to 30 days after the end of therapy (maximum six cycles of 21 days) regardless of ongoing ADT. The patients in the comparator arm of the STAMPEDE study were followed up after completion of the ADT. The follow-up started up to 30 days after completion and lasted at least 2 years. The observation period for SAE and severe AE (CTCAE grade ≥ 3) in the intervention arm of the STAMPEDE study (maximum of 6 to 7 months from randomisation) is thus considerably shorter than in the comparator arm. Furthermore, with regard to potential biases of these endpoints, it should be noted that the STAMPEDE study, in contrast to the TITAN study, is an unblinded study. For the two endpoints, the STAMPEDE study assumes a low risk of bias but only a sufficiently reliable effect estimate for the period of about six to seven months from randomisation.

On the results of the adjusted indirect comparison for SAE and severe AE (CTCAE grade ≥ 3)

For the endpoint SAE, the adjusted indirect comparison shows a statistically significant difference in favour of apalutamide in combination with ADT compared with docetaxel in combination with ADT and prednisolone with an effect estimate of HR: 0.10; 95% CI: 0.06; 0.17. Given the magnitude of this effect, it is not considered that this advantage in the case of SAE is entirely called into question by potential biases. In contrast, the effect estimate for the indirect comparison for the endpoint severe AE (CTCAE grade ≥ 3) is not regarded as sufficiently reliable in terms of results when taking into account the uncertainties mentioned above.

Therapy discontinuation because of adverse events

For the endpoint therapy discontinuation because of adverse events, data from the TITAN study are available only for the intervention side of the indirect comparison. An adjusted indirect comparison is therefore not possible.

In the overview of the results on side effects, results from the adjusted indirect comparison are available only for the endpoint SAE. Although these show a beneficial effect for apalutamide in combination with ADT, this can only be inferred for the first six to seven months after the start of therapy because of the observation periods in the arms of the STAMPEDE study. No statements beyond this period can be made for the endpoint SAE. Further results on endpoints in the side effects, symptomatology, or quality of life category that could be used to interpret this effect or would support it are not available from the adjusted indirect comparison. Taking into account the aforementioned uncertainties, an additional benefit for apalutamide in combination with ADT can thus not be derived with the required degree of certainty for the endpoint category side effects.

Overall assessment

For the assessment of the additional benefit of apalutamide in combination with ADT for the treatment of adult men with metastatic hormone sensitive prostate cancer (mHSPC), there are results on mortality, morbidity, and side effects compared with the appropriate comparator therapy docetaxel in combination with ADT and prednisolone.

The present assessment is based on an adjusted indirect comparison (according to Bucher) of the TITAN (apalutamide + ADT vs. ADT) and STAMPEDE (docetaxel + ADT + prednisolone) studies. Apalutamide in combination with ADT was compared via the bridge comparator ADT with docetaxel in combination with ADT and prednisolone.

For the endpoint overall survival, the adjusted indirect comparison shows no statistically significant difference between apalutamide in combination with ADT and docetaxel in combination with ADT and prednisolone. An additional benefit of apalutamide in combination with ADT is therefore not proven in the mortality category.

In the endpoint category morbidity, it is not assumed that the two studies are sufficiently similar for the endpoint time to 1st skeletal event. There are thus no usable data for an adjusted indirect comparison.

Similarly, with regard to health-related quality of life, there are no usable data for indirect comparison because in the TITAN and STAMPEDE studies, different instruments were used to collect data.

With regard to side effects, the adjusted indirect comparison can provide information only for the endpoint SAE. Although an effect in favour of apalutamide in combination with ADT has been shown, this can be inferred only for the first six to seven months after starting therapy. No statements beyond this period can be made for the endpoint SAE. Further results on endpoints in the side effects, symptomatology, or quality of life category that could be used to interpret this effect or would support it are not available. An additional benefit for apalutamide in combination with ADT in the side effects category can therefore not be derived with the necessary certainty.

In its overall assessment, the G-BA therefore concludes that an additional benefit of apalutamide in combination with ADT compared with docetaxel in combination with ADT and prednisolone for the treatment of adult men with metastatic hormone-sensitive prostate carcinoma (patients with distant metastases (M1 stage) and good general condition (according to ECOG/WHO 0 to 1 or Karnofsky Index ≥ 70%)) is not proven.

2.1.4 Summary of the assessment

This assessment refers to the benefit assessment of a new therapeutic indication for the active ingredient apalutamide:

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

The following were determined as an appropriate comparator therapy:

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

  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)

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In order to prove the additional benefit, the pharmaceutical company makes an adjusted indirect comparison according to Bucher.

For the endpoint overall survival, there is no statistically significant difference between apalutamide in combination with ADT and docetaxel in combination with ADT and prednisolone.

In the endpoint category morbidity and with regard to health-related quality of life, there are no data that can be used for an adjusted indirect comparison.

In terms of side effects, apalutamide in combination with ADT has an advantage only for the endpoint serious AE. However, this does not allow an additional benefit to be derived with sufficient certainty in terms of side effects overall.

In the overall view, an additional benefit for apalutamide in combination with ADT (for patients with distant metastases (M1 stage) and good general condition (according to ECOG/WHO 0 to 1 or Karnofsky Index ≥ 70%)) 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 the derivation, the pharmaceutical company adds up the numbers of newly diagnosed patients with remove metastases with the number of patients who were diagnosed at an earlier stage and newly develop distant metastases in the year under consideration and are not resistant to castration. This means that patients from previous years with mHSPC who have not developed resistance to ADT and who are eligible for therapy with apalutamide are not included. Furthermore, the information used to determine the latter proportion is based on data for which the assessment of metastasis was made only six weeks after the onset of ADT. This neglects patients who developed metastasis after ADT only after this period.

These figures do not include any restrictions regarding general condition (according to ECOG/WHO or Karnofsky Index ≥ 70%) and also include patients with poor general condition.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Erleada® (active ingredient: apalutamide) at the following publicly accessible link (last access: 23 June 2020):

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

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

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

2.4 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 August 2020).

Treatment duration:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements of adult men were used as a basis (average height: 1.79 m, average body weight: 85 kg). From this, a body surface area of 2.04 m² is calculated (calculation according to Du Bois 1916).[3]

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Apalutamide	continuously, 1 × daily	365	1	365
ADT				
Buserelin	continuously, every 3 months	4	1	4
Goserelin	continuously, every 3 months	4	1	4
Leuprorelin	continuously, every 3 months	4	1	4
Triptorelin	continuously, 1 × every 6 months	2	1	2
Degarelix	continuously, 1 × monthly	12	1	12
Orchiectomy	one-time	1	3.8 days average retention time	-
Appropriate comparator therapy				
ADT				
Buserelin	continuously, every 3 months	4	1	4
Goserelin	continuously,	4	1	4

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

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
	every 3 months			
Leuprorelin	continuously, every 3 months	4	1	4
Triptorelin	continuously, 1 × every 6 months	2	1	2
Degarelix	continuously, 1 × monthly	12	1	12
Orchiectomy	one-time	1	3.8 days average retention time	-
In combination with docetaxel with or without prednis(ol)one				
Docetaxel	1 × every 21 days	6	1	6
Possibly prednis(ol)one	2 × daily	252	1	126
In combination with abiraterone acetate in combination with prednis(ol)one				
Abiraterone acetate	continuously, 1 × daily	365	1	365
Prednis(ol)one	continuously, 1 × daily	365	1	365

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Apalutamide	240 mg	240 mg	4 × 60 mg	365	1460 × 60 mg
ADT					
Buserelin	9.45 mg	9.45 mg	1 × 9.45 mg	4	4 × 9.45 mg

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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 therapy					
ADT					
Buserelin	9.45 mg	9.45 mg	1 × 9.45 mg	4	4 × 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 × 10.8 mg	4	4 × 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 × 11.25 mg	4	4 × 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 × 22.5 mg	2	2 × 22.5 mg
Degarelix	80 mg	80 mg	1 × 80 mg	12	12 × 80 mg
Orchiectomy	One-time intervention				
In combination with docetaxel with or without prednis(ol)one					
Docetaxel	75 mg/m² BSA	153 mg	1 × 160 mg	6	6 × 160 mg
Possibly prednis(ol)one	5 mg	10 mg	2 × 5 mg	126	252 × 5 mg
In combination with abiraterone acetate and prednis(ol)one					
Abiraterone acetate	1,000 mg	1,000 mg	2 × 500 mg	365	730 × 500 mg
Prednis(ol)one	5 mg	5 mg	1 × 5 mg	365	365 × 5 mg

Costs:

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

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Apalutamide	112 FCT	€ 4,039.40	€ 1.77	€ 233.38	€ 3,804.25
Buserelin 9.45 mg three-month implant	2 PS	€ 1,001.96	€ 1.77	€ 56.30	€ 943.89
Goserelin 10.8 mg three-month implant	2 IMP	€ 987.74	€ 1.77	€ 55.49	€ 930.48
Leuprorelin 11.25 mg three-month implant	2 IMP	€ 712.09	€ 1.77	€ 86.93	€ 623.39
Triptorelin 22.5 mg	1 DSS	€ 920.37	€ 1.77	€ 51.66	€ 866.94
Degarelix 80 mg	3 PSI	€ 556.97	€ 1.77	€ 31.02	€ 524.18
Orchiectomy	-	-	-	-	Costs[4]: € 3,293.26
Appropriate comparator therapy					
Buserelin 9.45 mg three-month implant	2 PS	€ 1,001.96	€ 1.77	€ 56.30	€ 943.89
Goserelin 10.8 mg three-month implant	2 IMP	€ 987.74	€ 1.77	€ 55.49	€ 930.48
Leuprorelin 11.25 mg three-month implant	2 IMP	€ 712.09	€ 1.77	€ 86.93	€ 623.39
Triptorelin 22.5 mg	1 DSS	€ 920.37	€ 1.77	€ 51.66	€ 866.94
Degarelix 80 mg	3 PSI	€ 556.97	€ 1.77	€ 31.02	€ 524.18
Orchiectomy	-	-	-	-	Costs[4]: € 3,293.26
Abiraterone acetate	56 FCT	€ 3,429.77	€ 1.77	€ 0.00	€ 3,428.00
Docetaxel[5]	1 CIS	€ 1,362.13	€ 1.77	€ 175.44	€ 1,184.92
Prednisone[6]	100 TAB	€ 16.05	€ 1.77	€ 0.43	€ 13.85

[4] DRG M04B Basic remuneration; Last updated: July 2020 (Source: https://www.drg-research-group.de/index.php)

[5] The costs are presented on the basis of low-cost medicinal product also taking into account the requirements of Section 129 SGB V and the possibility of prescribing medicinal products under their active ingredient designation. The corresponding medicinal products must nevertheless be prescribed taking into account the respective approved therapeutic indications.

[6] Fixed reimbursement rate

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Prednisolone[6]	100 TAB	€ 14.78	€ 1.77	€ 0.33	€ 12.68
Abbreviations: PS = prefilled syringes; FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; PSI = powder and solvent for solution for injection; IMP = implant; TAB = tablets; DSS = dry substance with solvent					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 August 2020

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be assessed and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

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

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) 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 special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: 11. Supplementary Agreement of 1 March 2020 to the contract on price formation for substances and preparations of substances), surcharges for the preparation of parenteral preparations containing cytostatics of a maximum of € 81 per ready-to-use preparation and for the preparation of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall apply. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating 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 ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

3. Bureaucratic costs

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

4. Process sequence

At its session on 27 January 2015, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products redefined the appropriate comparator therapy at its session on 28 January 2020.

On 24 February 2020, the pharmaceutical company submitted a dossier for the benefit assessment of apalutamide to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 25 February 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient apalutamide.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 May 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 2 June 2020. The deadline for submitting written statements was 23 June 2020.

The oral hearing was held on 6 July 2020.

By letter dated 28 July 2020, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 6 August 2020.

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

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 11 August 2020, and the proposed resolution was approved.

At its session on 20 August 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	27 January 2015	Determination of the appropriate comparator therapy
Subcommittee on Medicinal	28 January 2020	Redefinition of the appropriate comparator therapy

Products		
Working group Section 35a	1 July 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	6 July 2020	Conduct of the oral hearing
Working group Section 35a	14 July 2020 21 July 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	28 July 2020	Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	4 August 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	11 August 2020	Concluding discussion of the draft resolution
Plenum	20 August 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 20 August 2020

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

Prof. Hecken