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 Darolutamide (Non-metastatic Castration Resistant Prostate Cancer)

of 15 October 2020

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of 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 proof and published on the internet.

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

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient darolutamide in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 May 2020. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 29 April 2020.

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 3 August 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 brigatinib compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has 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 darolutamide.

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 darolutamide (Nubeqa) in accordance with the product information

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

2.1.2 Appropriate comparator therapy

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

Appropriate comparator therapy:

A wait-and-see approach while maintaining the existing conventional androgen deprivation therapy (ADT)

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

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

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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: Apalutamide, bicalutamide, flutamide, cyproterone acetate, enzalutamide, degarelix, buserelin, goserelin, leuprorelin, triptorelin, and estramustin (cytostatic agent).

[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.

On 2. In principle, radiotherapy and surgical treatment can be considered as non-medical therapies for non-metastatic prostate cancer. It is assumed that percutaneous radiotherapy is excluded as a possibility for patients who are undergoing therapy. This also applies to surgical therapy, which is why the non-medicinal treatments described above are not considered as appropriate comparator therapies.

On 3. The following resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V are available.

- Apalutamide: Resolution of 1 October 2020
- Enzalutamide: Resolution of 16 May 2019 (limited until 15 May 2020, currently reassessment after deadline)

The G-BA is assessing non-medicinal treatments such as interstitial brachytherapy for localised prostate cancer and proton therapy for prostate cancer as new methods for diagnosis and treatment. Both assessment procedures are currently on hold (Resolution of 17 December 2009/Resolution of 19 June 2008).

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

Thus, the evidence for treatment options in the present therapy situation is very limited. No relevant Cochrane reviews or systematic reviews were identified. The data basis on the question of whether medicinal androgen deprivation should be continued unchanged, modified, or discontinued in the present therapy situation is both qualitatively weak and contradictory. However, the current guidelines predominantly recommend a wait-and-see approach with continuation of ADT.

With regard to secondary hormone manipulation, the active ingredients apalutamide and enzalutamide were assessed in the present therapeutic indication within the scope of the benefit assessment according to Section 35a SGB V. In the reassessment of apalutamide after the deadline, there was an indication of a minor additional benefit compared with a wait-and-see approach while maintaining the existing ADT (resolution of 1 October 2020). With regard to this recently completed benefit assessment procedure, no new definition of appropriate comparator therapy has been made in the present resolution for the purpose of defining the appropriate comparator therapy. The benefit assessment of enzalutamide revealed that there was no additional benefit compared with wait-and-see approach while maintaining the existing ADT (resolution of 16 May 2019). The resolution on enzalutamide was limited until 15 May 2020. A post-closure reassessment of the active ingredient enzalutamide will therefore be carried out simultaneously with the present benefit assessment procedure. For these reasons, apalutamide and enzalutamide are not identified as appropriate comparator therapies for the present assessment.

For the remaining antiandrogens, there is no proof of efficacy in clinically relevant endpoints. Chemotherapy is not recommended to treat non-metastatic castration resistant prostate cancer.

Based on the evidence available, the G-BA considers the wait-and-see approach while maintaining the existing conventional androgen deprivation therapy to be the most appropriate comparator therapy in the treatment of adult men with non-metastatic castration resistant prostate cancer.

Conventional ADT in treating the condition implies surgical castration or pharmacological castration with GnRH agonists or GnRH antagonists.

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

2.1.3 Extent and probability of the additional benefit

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

For adult men with non-metastatic castration resistant prostate cancer (nm-CRPC) who are at high risk of developing metastatic disease, there is an indication of a considerable additional benefit.

Justification:

The benefit assessment of darolutamide is based on results of the pivotal, randomised, double-blind Phase III ARAMIS study. This is an ongoing, international, multi-centre study that is being conducted in 36 countries and 409 study centres.

Included were adult men with non-metastatic castration resistant prostate cancer who are at high risk of developing metastatic disease The presence of a high risk for the development of metastases was defined by a prostate-specific antigen (PSA) doubling time (PSADT) of ≤ 10 months. In addition, a PSA value ≥ 2 ng/ml had to be present at the time of screening.

The 1509 patients included in the study were randomised to the darolutamide (N = 955) or placebo arm (N = 554) at a ratio of 2:1. In both treatment arms, androgen deprivation therapy with a gonatropin-releasing hormone (GnRH) agonist or antagonist was also carried out or continued if there was no bilateral orchiectomy. The randomisation was stratified by bone-protective substances (yes / no) and PSADT (≤ 6 months / > 6 months).

Based on the investigation regime carried out in the study, the comparison with placebo + ADT is regarded as a sufficient approximation to the appropriate comparator therapy of a wait-and-see approach while maintaining the existing conventional ADT.

The patients had a median age of 74 years at the time of study inclusion; the vast majority were from Europe (approx. 64%), and the median first diagnosis of prostate cancer was made about seven years before randomisation to the study.

The primary endpoint of the study is metastasis-free survival (MFS). Furthermore, overall survival, endpoints on morbidity, health-related quality of life, and adverse events, among others, are surveyed.

Patients are treated until documented radiographic progression, occurrence of unacceptable toxicity, or withdrawal of informed consent.

In the study, there are no restrictions regarding the type of follow-up therapy after the end of treatment. At the time of the first data cut-off, 10.5% of patients in the darolutamide arm and 23.5% of patients in the control arm received systemic follow-up therapy. The most common follow-up treatments administered in the study were abiraterone acetate, docetaxel, and enzalutamide.

Patients from both study arms had the option of being treated with darolutamide + ADT unblinded after unblinding of the study. At the time of unblinding, 200 patients in the control arm were still receiving treatment. Of these, 170 patients (a total of 30.7% of patients randomised to the control arm) switched to treatment with darolutamide + ADT.

In the study, there was a high proportion of patients who discontinued therapy. Moreover, significantly more patients in the control arm than in the intervention arm discontinued therapy. In addition to a confirmed metastasis, therapy was discontinued at the investigator's discretion or for personal reasons.

Follow-up is provided for overall survival and morbidity endpoints (except health status) until death or end of study. Health status and health-related quality of life endpoints (except for the prostate cancer-specific sub-scale [PCS] of the Functional Assessment of Cancer Therapy – Prostate [FACT-P]) were monitored for all patients until the end of the double-blind treatment. In addition, patients in the intervention arm who continue darolutamide + ADT in the unblinded treatment phase will be followed until 28 days after the end of treatment. For the PCS of the

FACT-P, patients are followed until death or the end of study. For the endpoints in the side effects category, follow-up was performed for all patients until the end of double-blind treatment. Patients receiving darolutamide + ADT after the unblinded treatment phase will be followed up until 28 days after the end of treatment. Patients who discontinue therapy with the study medication before confirmed metastasis and are treated with a follow-up therapy prohibited by the study design (including immunotherapy, cytotoxic chemotherapy, and other systemic antineoplastic therapies) will not be monitored for any endpoints except for overall survival.

Two data cut-offs are available for the study. The first data cut-off of 3 September 2018 is the *a priori* planned primary evaluation at the end of the double-blind phase. The later data cut-off of 15 November 2019 represents the final analysis for all endpoints after 240 deaths. For the benefit assessment, the first data cut-off of 3 September 2018 was used for all endpoints. In addition, for the overall survival endpoint, the results of the later data cut-off of 15 November 2019 are used. For the other endpoints, the results of this later data cut-off are not usable, particularly because of the systematic shortening of the observation period described above (patients who discontinue treatment with the study medication before confirmed metastasis and receive a follow-up therapy prohibited by the study plan) as well as the unsystematic monitoring after the end of double-blind treatment. Furthermore, evaluations for this data cut-off are not available for all endpoints used.

Extent and probability of the additional benefit

Mortality

Overall survival

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

For the overall survival endpoint, both the first and second data sets show a statistically significant difference between treatment arms in favour of darolutamide. In both the darolutamide and placebo arm, the median time to the event was not yet reached.

Although darolutamide leads to an improvement in overall survival, the extent of the effect of darolutamide compared with the wait-and-see approach, taking into account the remaining life expectancy of patients in the present therapy situation, is considered a relevant – but no more than a minor – improvement. In addition, the results for the overall survival endpoint in both study arms are based on low event rates.

Morbidity

Metastasis-free survival (MFS)

In the ARAMIS study, the MFS endpoint was defined as the time from randomisation to first occurrence (according to RECIST1.1 criteria) of a confirmed radiographically detectable bone, soft-tissue bone metastasis, or death.

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

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

The morbidity component was not calculated on the basis of symptoms but rather solely on the basis of imaging techniques (radiographic detection of metastasis) and thus solely on the basis of primarily asymptomatic findings and not directly patient-relevant findings.

A direct assessment of the metastasis of the disease by means of a symptomatology perceived by the patients is not possible using the operationalisation chosen here. A differentiation between symptomatic and asymptomatic metastases is therefore also not possible. Against

the background that metastasis is often asymptomatic in patients with castration resistant prostate cancer, this point should be considered as highly relevant. In this regard, guidelines consistently differentiate between symptomatic and asymptomatic or slightly symptomatic prostate cancer patients, with distinct therapy recommendations in each case.

In addition, metastasis in patients receiving treatment for non-metastatic castration resistant high-risk prostate cancer is not considered to be as prognostically relevant as it would be in other oncological indications, where metastasis potentially indicates treatment should be transitioned from curative to palliative care. The data available on the MFS endpoint indicate that darolutamide delays but does not prevent metastasis.

As a result, there are considerable uncertainties in the significance of the results for this endpoint for patient-relevant benefit, which is why the endpoint MFS is not used in the present assessment.

Symptomatic skeletal events

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

- external radiotherapy to alleviate skeletal symptoms
- new symptomatic, pathological bone fractures
- occurrence of a spinal cord compression
- tumour-related orthopaedic surgery

The patients in this therapeutic indication are in a palliative therapy situation. The control of symptoms and the maintenance of quality of life are therefore of particular importance. In the present operationalisation, the endpoint symptomatic skeletal events is considered patient-relevant. There is a statistically significant advantage of darolutamide compared with the wait-and-see approach for the combined endpoint. In both the darolutamide and placebo arm, the median time to the event was not yet reached. Evaluations are available for the individual components of the endpoint; these record only the first result within the combined endpoint. A statement on statistical differences in the individual components can therefore not be interpreted meaningfully.

Invasive procedures specific to prostate cancer

The endpoint collected in the ARAMIS study is defined as the time from randomisation to the start of the first invasive procedure specific to prostate cancer. An invasive procedure specific to prostate cancer was defined as any procedure used to relieve symptoms and signs and to diagnose disease progression (e.g. bladder catheterisation, nephrostomy, orchiectomy, prostatectomy, radiotherapy, surgical procedure excision/resection, transurethral resection of the bladder, transurethral resection of the prostate).

For the endpoint invasive procedures specific to prostate cancer, there is a statistically significant difference in favour of darolutamide compared with the wait-and-see approach. In both the darolutamide and placebo arm, the median time to the event was not yet reached.

Pain (BPI-SF, start of opioid therapy)

In the ARAMIS study, pain was assessed as a patient-reported endpoint using the Brief Pain Inventory – Short form (BPI-SF) questionnaire.

Pain progression

For the benefit assessment, the pharmaceutical company presented time-to-event analyses for pain progression operationalised as the time to first deterioration of Item 3 of the BPI-SF (worst pain within the last 24 hours) by ≥ 2 points compared with the start of study or the start of treatment with short- or long-acting opioids. In the ARAMIS study, the average of BPI-SF Item 3 of the last 7 days before the round, which takes place every 16 weeks, was determined.

This means that the BPI-SF surveys are conducted at long intervals. In contrast, the start of opioid therapy is continuously recorded in the study via the concomitant medication. With the continuous recording of opioid therapy, it is thus possible to record events that are not recorded via the BPI-SF because of the long time interval between surveys. Overall, there is a statistically significant difference in favour of darolutamide compared with the wait-and-see approach for the endpoint “pain progression”.

The non-specified evaluations on BPI-SF Item 3 (deterioration by ≥ 2 points) submitted by the pharmaceutical company without taking into account the start of opioid therapy are presented additionally.

Impairment because of pain

For the impairment of pain, items 9a-g are used for the assessment of the BPI-SF. Overall, based on the differences in mean values, the endpoint “impairment because of pain” showed a statistically significant difference in favour of darolutamide compared with the wait-and-see approach. In the written statement, the pharmaceutical company presents the standardised mean difference in the form of Hedges’ g. The 95% confidence interval of the standardised mean difference was not completely outside the irrelevance range of −0.2 to 0.2. Thus it cannot be deduced that the effect observed is relevant.

Pain intensity

Furthermore, evaluations of the BPI-SF for items 3-6 are available for pain intensity. The results for the endpoint are not taken into account for the present assessment; had they been, the findings for Item 3 would have been taken into account twice. They are therefore only presented additionally.

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

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

The pharmaceutical company presented time-to-event analysis for deterioration and improvement by ≥ 7 and ≥ 10 points. Because of the low return rates in the two treatment arms (11% in the intervention arm and 24% in the control arm) combined with the low survey times (Week 16 and individual end of treatment), these evaluations are not usable.

Furthermore, the pharmaceutical company presented evaluations of the mean change. For the present assessment, the evaluations of the mean change at Week 16 are used. These are based on sufficiently high return rates (91% in the intervention arm and 88% in the control arm). Based on the mean difference from Week 16, there is a statistically significant difference in favour of darolutamide. The standardised mean difference in the form of Hedges’ g is used to assess the relevance of the result. The 95% confidence interval of the standardised mean difference was not completely outside the irrelevance range of −0.2 to 0.2. Thus, it cannot be deduced that the effect observed is relevant.

EORTC QLQ-PR25

In the ARAMIS study, the disease-specific symptomatology of the patients were surveyed using the four symptom scales of the prostate cancer-specific questionnaire European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate25 (EORTC QLQ-PR25). This questionnaire is only valid when evaluated in combination with findings from the core questionnaire EORTC QLQ-C30. However, this questionnaire was not recorded in the study. Taken in isolation, EORTC QLQ-PR25 is therefore presented as being invalid as a comprehensive description of the symptomatology. This applies equally to both functional scales of the EORTC QLQ-PR25. For this reason, the results for EORTC QLQ-PR25 were not included in the current benefit assessment.

In the overall assessment of the endpoint category morbidity, statistically significant differences in favour of darolutamide were found for the endpoints symptomatic skeletal events, invasive

procedures specific to prostate cancer, and pain progression (measured using BPI-SF Item 3 and initiation of opioid therapy). Based on the data available, these effects are assessed overall as a significant improvement in disease-related symptomatology that has not yet been achieved. The attenuation of serious symptoms and the avoidance of invasive procedures specific to prostate cancer are considered to be of relevant importance in the present therapy situation.

Health-related quality of life

FACT-P

In the ARAMIS study, patients reported on their health-related quality of life via the FACT-P questionnaire. The FACT-P questionnaire consists of the cross-tumour disease questionnaire (FACT-G) and a prostate cancer specific sub-scale (PCS). The FACT-G questionnaire, in turn, consists of the four sub-scales physical well-being, social/family well-being, emotional well-being, and functional well-being.

Only the total score of the FACT-P questionnaire was considered in assessing the additional benefit because this provides a comprehensive overview of the data on the health-related quality of life of the patients. The individual sub-scales of the FACT-P are therefore presented additionally. The responder analyses submitted by the pharmaceutical company for the deterioration of the FACT-P overall score of ≥ 10 points are used. Usable data with sufficiently high return rates are available only for Week 16. At Week 16, the FACT-P total score between treatment arms showed a statistically significant difference in favour of darolutamide.

Overall, for health-related quality of life, there is a relevant improvement for darolutamide compared with the wait-and-see approach.

Side effects

Total adverse events (AE)

Almost all study participants experienced AE. The results are presented additionally.

Serious AE (SAE), severe AE (CTCAE grade ≥ 3), therapy discontinuations because of AE

For the endpoints SAE, severe AE (CTCAE grade ≥ 3), and therapy discontinuations because of AE, there are no statistically significant differences between the treatment arms.

Specific AE

For the specific AE, an advantage in the endpoint “Renal and urinary disorders (SOC, SAE)” is offset by a disadvantage in the endpoint “General disorders and administration site conditions (SOC, SAE)”.

In the overall assessment of the endpoint category side effects, neither an advantage nor a disadvantage can be identified for darolutamide compared with the wait-and-see approach. In detail, only the specific adverse events show differences. For darolutamide, there is an advantage for one endpoint and a disadvantage in another endpoint compared with the wait-and-see approach.

Overall assessment

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

In the ongoing study, darolutamide is compared with placebo. In both treatment arms, androgen deprivation therapy (ADT) was also carried out or continued if there was no bilateral orchiectomy. Based on the examination regimes carried out, the placebo comparison is

regarded as a sufficient approximation to the appropriate comparator therapy of a wait-and-see approach while maintaining the existing conventional ADT.

The improvement achieved by darolutamide in the endpoint category mortality compared with the wait-and-see approach is assessed as a relevant – but no more than minor – improvement, taking into account the remaining life expectancy of patients in the current therapy situation. Moreover, the results in both study arms are based on low event rates.

In the endpoint category morbidity, for the endpoints symptomatic skeletal events as well as invasive procedures specific to prostate cancer and pain progression (measured using BPI-SF Item 3 and initiation of opioid therapy), there were patient-relevant advantages from treatment with darolutamide. Based on the data of the morbidity endpoint category, the effects are assessed as a significant improvement in terms of symptomatology that has not yet been achieved. The attenuation of serious symptoms and the avoidance of invasive procedures specific to prostate cancer are considered to be of relevant importance in the present therapy situation.

For the present assessment, there is also data on health-related quality of life reported by patients and collected using the FACT-P prostate cancer-specific questionnaire. These show a relevant improvement in the health-related quality of life for darolutamide compared with the wait-and-see approach.

In terms of side effects, there is neither an advantage nor disadvantage of darolutamide compared with a wait-and-see approach. There are significant differences only in the specific adverse events. For darolutamide, there is an advantage for one endpoint and a disadvantage in another endpoint compared with the wait-and-see approach.

In the overall analysis of the results for the patient-relevant endpoints, only advantages of darolutamide compared with the wait-and-see approach are shown in the endpoint categories mortality, morbidity, and health-related quality of life. There are no disadvantages in terms of side effects. Overall, there is a significant improvement in the therapy-relevant benefit that has not yet been achieved.

As a result, for darolutamide for the treatment of adult men with non-metastatic castration resistant prostate cancer (nm-CRPC) who are at high risk of developing metastatic disease, the G-BA found considerable additional benefit compared with the appropriate comparator therapy of a wait-and-see approach while maintaining the existing conventional ADT.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, double-blind, placebo-controlled, phase III ARAMIS study. The risk of bias at the study level is classified as low.

Because the benefit assessment is based on the results of only one study, at best indications of an additional benefit can be derived with regard to the reliability of data.

Because of the return rates, the results on health status and health-related quality of life refer to a short observation period (evaluations for Week 16) and are therefore limited in terms of significance.

The uncertainties described are not considered to be so severe that a downgrading of the reliability of data in the overall assessment would be justified. Based on the proof available, the reliability of data is thus classified in the “indication” category.

2.1.4 Summary of the assessment

The present assessment refers to the benefit assessment of the new medicinal product Nubeqa with the active ingredient darolutamide.

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

The G-BA determined that the wait-and-see approach, while maintaining the existing conventional androgen deprivation (ADT), was an appropriate comparator therapy.

In the randomised, double-blind ARAMIS study, patients were randomised to either the darolutamide or placebo arm. In both arms, androgen deprivation therapy was also maintained if there was no bilateral orchiectomy. The investigation regimes carried out in the ARAMIS study are considered a sufficient approximation to the appropriate comparator therapy.

The improvement in overall survival achieved by apalutamide compared with the wait-and-see approach is assessed as a relevant – but no more than minor – improvement, taking into account the remaining life expectancy of patients in the present therapy situation. Moreover, the results in both study arms are based on low event rates.

In the endpoint category morbidity, for the endpoints symptomatic skeletal events as well as invasive procedures specific to prostate cancer and pain progression (measured using BPI-SF Item 3 and initiation of opioid therapy), there were patient-relevant advantages from treatment with darolutamide. Based on the data of the morbidity endpoint category the effects are assessed as a significant improvement in terms of symptomatology that has not yet been achieved. The attenuation of serious symptoms and the avoidance of invasive procedures specific to prostate cancer are considered to be of relevant importance in the present therapy situation.

There is also data on health-related quality of life reported by patients and collected using the FACT-P prostate cancer-specific questionnaire. These show a relevant improvement in the health-related quality of life for darolutamide compared with the wait-and-see approach.

In terms of side effects, there is neither an advantage nor a disadvantage for darolutamide compared with the wait-and-see approach. The specific adverse events alone show an advantage for one endpoint and a disadvantage for darolutamide compared with the wait-and-see approach for another endpoint.

Overall, in the endpoint categories of mortality, morbidity, and health-related quality of life, there are only advantages of darolutamide compared with the wait-and-see approach. There are no disadvantages in terms of side effects. Overall, there is a significant improvement in the therapy-relevant benefit that has not yet been achieved.

In the overall view, there is an indication of a considerable additional benefit of darolutamide compared with the monitoring wait-and-see approach.

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

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

The patient numbers specified by the pharmaceutical company in the dossier are based on the resolution on apalutamide of 1 August 2019 and enzalutamide of 16 May 2019 in the present therapeutic indication. However, these are subject to uncertainties. It is generally assumed that the stated number of patients is an underestimate because the derivation of patient numbers is based on data on the 5-year prevalence, which does not take sufficient account of all patients with prostate cancer.

In order to enable a consistent consideration of patient numbers in view of these uncertainties, taking into account the most recent resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the present therapeutic indication, this resolution is based on the relevant information from the resolution on apalutamide of 1 October 2020.

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 Nubeqa® (active ingredient: darolutamide) at the following publicly accessible link (last access: 31 August 2020):

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

Treatment with darolutamide 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.

Medicinal castration with a luteinising hormone releasing hormone (LHRH) analogue 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: 15 September 2020).

Treatment duration:

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

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Darolutamide	continuously, 2 × daily	365	1	365
ADT				
Degarelix	continuously, 1 × per month	12	1	12
Leuprorelin	continuously, every 3 months	4	1	4
Buserelin	continuously, every 3 months	4	1	4

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Goserelin	continuously, every 3 months	4	1	4
Triptorelin	continuously, 1 × every 6 months	2	1	2
Appropriate comparator therapy				
ADT				
Degarelix	continuously, 1 × per month	12	1	12
Leuprorelin	continuously, every 3 months	4	1	4
Buserelin	continuously, every 3 months	4	1	4
Goserelin	continuously, every 3 months	4	1	4
Triptorelin	continuously, 1 × every 6 months	2	1	2

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Darolutamide	600 mg	1200 mg	4 × 300 mg	365	1460 × 300 mg

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
ADT					
Degarelix	80 mg	80 mg	1 × 80 mg	12	12 × 80 mg

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Leuprorelin	11.25 mg	11.25 mg	1 × 11.25 mg	4	4 × 11.25 mg
Buserelin	9.45 mg	9.45 mg	1 × 9.45 mg	4	4 × 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 × 10.8 mg	4	4 × 10.8 mg
Triptorelin	22.5 mg	22.5 mg	1 × 22.5 mg	2	2 × 22.5 mg
Appropriate comparator therapy					
ADT					
Degarelix	80 mg	80 mg	1 × 80 mg	12	12 × 80 mg
Leuprorelin	11.25 mg	11.25 mg	1 × 11.25 mg	4	4 × 11.25 mg
Buserelin	9.45 mg	9.45 mg	1 × 9.45 mg	4	4 × 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 × 10.8 mg	4	4 × 10.8 mg
Triptorelin	22.5 mg	22.5 mg	1 × 22.5 mg	2	2 × 22.5 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					
Darolutamide 300 mg	112 FCT	€ 4,703.71	€ 1.77	€ 272.30	€ 4,429.64
Degarelix 80 mg	3 PSI	€ 556.97	€ 1.77	€ 31.02	€ 524.18
Leuprorelin 11.25 mg three-month implant	2 IMP	€ 712.09	€ 1.77	€ 86.93	€ 623.39
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
Triptorelin 22.5 mg	1 DSS	€ 920.37	€ 1.77	€ 51.66	€ 866.94
Appropriate comparator therapy					

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
Degarelix 80 mg	3 PSI	€ 556.97	€ 1.77	€ 31.02	€ 524.18
Leuprorelin 11.25 mg three-month implant	2 IMP	€ 712.09	€ 1.77	€ 86.93	€ 623.39
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
Triptorelin 22.5 mg	1 DSS	€ 920.37	€ 1.77	€ 51.66	€ 866.94

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 September 2020

Costs for additionally required SHI services:

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

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

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

3. Bureaucratic costs

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

4. Process sequence

At its session on 22 October 2013, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 29 April 2020, the pharmaceutical company submitted a dossier for the benefit assessment of darolutamide to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 29 April 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 darolutamide.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 July 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 3 August 2020. The deadline for submitting written statements was 24 August 2020.

The oral hearing was held on 8 September 2020.

By letter dated 8 September 2020, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 25 September 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 6 October 2020, and the proposed resolution was approved.

At its session on 15 October 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	22 October 2013	Determination of the appropriate comparator therapy
Working group Section 35a	1 September 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	8 September 2020	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	15 September 2020 29 September 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	6 October 2020	Concluding discussion of the draft resolution
Plenum	15 October 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 15 October 2020

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

Prof. Hecken