Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Relugolix (Prostate cancer, advanced, hormone-sensitive)

of 6 April 2023

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 the 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 online and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient relugolix on 15 October 2022 in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. 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 13 October 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 16 January 2023 on the G-BA website (www.g-ba.de), 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 relugolix 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, as well the addendum drawn up by the G-BA on the benefit assessment. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of relugolix.

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

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

2.1.1 Approved therapeutic indication of Relugolix (Orgovyx) in accordance with the product information

Relugolix is indicated for the treatment of adult patients with advanced hormone-sensitive prostate cancer.

Therapeutic indication of the resolution (resolution of 6 April 2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Patients with advanced hormone-sensitive prostate cancer who are eligible for local therapy

Appropriate comparator therapy for relugolix as monotherapy:

- Radical prostatectomy, if necessary in combination with lymphadenectomy

  or

- Percutaneous radiotherapy in combination with conventional androgen deprivation or bicalutamide

  or

- Percutaneous radiotherapy in combination with HDR brachytherapy (only for patients in clinical category cT3)

b) Patients with advanced hormone-sensitive prostate cancer who are ineligible for local therapy

Appropriate comparator therapy for relugolix as monotherapy:

- Conventional androgen deprivation

  or

- bicalutamide

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

c) Patients with advanced hormone-sensitive prostate cancer and PSA recurrence or clinical recurrence after primary local therapy

Appropriate comparator therapy for relugolix as monotherapy:

- Patient-individual therapy with selection of:
  - salvage prostatectomy,
  - percutaneous salvage radiotherapy and
  - percutaneous salvage radiotherapy in combination with conventional androgen deprivation or bicalutamide;

  taking into account prior therapy and risk of progression.

d) Patients with metastatic hormone-sensitive prostate cancer (mHSPC)

d1) Patients with metastatic hormone-sensitive prostate cancer (mHSPC) who are eligible for combination regimen

Appropriate comparator therapy for relugolix as monotherapy:

- Conventional androgen deprivation in combination with apalutamide

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

  or
- conventional androgen deprivation in combination with docetaxel with or without prednisone or prednisolone

  or
- conventional androgen deprivation in combination with enzalutamide

d2) Patients with metastatic hormone-sensitive prostate cancer (mHSPC) who are ineligible for combination regimen

Appropriate comparator therapy for relugolix as monotherapy:

- Conventional androgen deprivation

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

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

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

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

2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA 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 active ingredients bicalutamide, cyproterone acetate, flutamide, degarelix, buserelin, goserelin, leuprorelin, triptorelin, abiraterone acetate, apalutamide, enzalutamide and docetaxel are approved in the present therapeutic indication.

on 2. Non-medicinal treatment options in the present therapeutic indication are basically orchiectomy, brachytherapy, percutaneous radiotherapy and prostatectomy (if necessary, with lymphadenectomy).

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

- abiraterone acetate (resolution of 07.06.2018)
- apalutamide (resolution of 20.08.2020)
- enzalutamide (resolution of 19.11.2021)

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy").

With regard to the present therapeutic indication, it should first be noted that the recommendations of the guidelines differentiate according to whether patients with advanced hormone-sensitive prostate cancer already have a distant metastasis (M1) or not yet.

If there is no distant metastasis (M1), guidelines for patients with advanced hormone-sensitive prostate cancer further distinguish whether the patients are initially eligible for local therapy or whether initial local therapy has already been administered and a PSA recurrence or clinical recurrence has occurred. Therefore, when determining the appropriate comparator therapy, corresponding, distinct patient groups are taken into account.

Overall, when determining the appropriate comparator therapy, it is assumed that the individual therapeutic decision in the target population was made against long-term observation. Monitoring wait-and-see approach is therefore not considered to be an appropriate comparator therapy in the present case.

a) Patients eligible for local therapy

For patients with advanced hormone-sensitive prostate cancer who are eligible for local therapy, the guidelines unanimously recommend radical prostatectomy, which can also be combined with lymphadenectomy, depending on an affected local lymph node. As an alternative to radical prostatectomy, percutaneous radiotherapy in combination with conventional androgen deprivation or the active ingredient bicalutamide is considered to be of equal significance in the available evidence. Only for patients in clinical category cT3, percutaneous radiotherapy in combination with HDR brachytherapy is also recommended as a further treatment option.

Overall, the G-BA therefore considers it appropriate for patients with advanced hormone-sensitive prostate cancer who are eligible for local therapy to undergo radical prostatectomy, if necessary in combination with lymphadenectomy or percutaneous radiotherapy in combination with conventional androgen deprivation or bicalutamide or (only for patients in clinical category cT3) percutaneous radiotherapy in combination with HDR brachytherapy as equally appropriate comparator therapies.

b) Patients who are ineligible for local therapy

For patients with advanced hormone-sensitive prostate cancer who are ineligible for local therapy, the unanimous recommendation is to perform conventional androgen deprivation. With regard to this group of patients, this also corresponds to the written statements of the scientific-medical societies. According to the available evidence, the active ingredient bicalutamide is also an equivalent treatment option. Conventional androgen deprivation or bicalutamide are therefore determined to be equally appropriate comparator therapies for this patient group.

c) Patients with PSA recurrence or clinical recurrence after primary local therapy

For patients with advanced hormone-sensitive prostate cancer and PSA recurrence or clinical recurrence after primary local therapy, the choice of further treatment is largely determined by the prior therapy and the risk of progression. For example, percutaneous salvage radiotherapy is recommended for patients who have undergone an initial radical prostatectomy; depending on the risk of progression, this can also be combined with conventional androgen deprivation or the active ingredient bicalutamide. Conversely, salvage prostatectomy is recommended for patients who have initially undergone percutaneous radiotherapy. However, according to the available evidence, (sole) hormone ablative therapy for PSA recurrence or PSA progression does not represent standard therapy.

In summary, the G-BA therefore determines a patient-individual therapy as an appropriate comparator therapy for this patient group, choosing between salvage prostatectomy, percutaneous salvage radiotherapy and percutaneous salvage radiotherapy in combination with conventional androgen deprivation or bicalutamide, taking into account the prior therapy and the risk of progression.

d) Patients with metastatic hormone-sensitive prostate cancer

If distant metastasis (M1) is already present, the recommendations of the guidelines for patients with metastatic hormone-sensitive prostate cancer (mHSPC) differentiate according to whether the patients are eligible for combination regimen. For patients with mHSPC who are eligible for combination regimen (patient group d1), the guidelines are unanimously in favour of therapy with apalutamide, enzalutamide or abiraterone acetate or chemotherapy with docetaxel in addition to conventional androgen deprivation. The background to these recommendations is that, compared with conventional ADT alone, relevant advantages in therapeutic benefit have been shown both by combination with docetaxel and with the other therapies mentioned.

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

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

In the corresponding benefit assessment on abiraterone acetate, an indication of a considerable additional benefit of combination therapy with ADT and prednisone or prednisolone compared to conventional ADT was identified for patients with newly diagnosed high-risk, metastatic prostate cancer (resolution of 07.06.2018). In the benefit assessment of apalutamide in combination with ADT, no additional benefit was identified for patients with distant metastases (M1 stage) and good general condition (0 to 1 according to ECOG / WHO or ≥ 70 % according to Karnofsky index), compared to docetaxel in combination with prednisolone and ADT (resolution of 20.08.2020). Likewise, the G-BA did not identify any additional benefit of enzalutamide in combination with ADT over docetaxel in combination with prednisolone and ADT for patients with distant metastases (M1 stage) and good general condition (0 to 1 according to ECOG / WHO or ≥ 70% according to Karnofsky index) (resolution of 15.12.2021).

In the overall analysis of the available evidence, the treatment options apalutamide, enzalutamide, abiraterone acetate with prednisone or prednisolone, and docetaxel with or without prednisone or prednisolone - each of the treatment options in combination with conventional androgen deprivation - are considered equally appropriate comparator therapies. According to the marketing authorisation, abiraterone acetate with prednisone or prednisolone in combination with conventional androgen deprivation is only indicated for patients with newly diagnosed high-risk prostate cancer.

Only for patients with mHSPC who are ineligible for combination regimen, guidelines recommend the implementation of conventional androgen deprivation alone, which is accordingly determined by the G-BA as an appropriate comparator therapy for patient group d2).

According to the generally recognised state of medical knowledge, conventional androgen deprivation alone is only indicated for patients with mHSPC (patient group d2) who are ineligible for combination therapy - add-on therapy to conventional androgen deprivation - with regard to any comorbidities and their general condition.

In the context of the present therapeutic indication, conventional androgen deprivation therapy refers to surgical or medicinal castration by therapy with GnRH agonists or GnRH antagonists.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5, Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

a) Patients with advanced hormone-sensitive prostate cancer who are eligible for local therapy

An additional benefit is not proven.

Justification:

For the treatment of adult males with advanced hormone-sensitive prostate cancer who are eligible for local therapy, the pharmaceutical company does not submit any data for the assessment of additional benefit. Therefore, an additional benefit is not proven.

b) Patients with advanced hormone-sensitive prostate cancer who are ineligible for local therapy

Justification:

To demonstrate an additional benefit of relugolix for the treatment of adult males who are ineligible for local therapy, the pharmaceutical company presents the results of the HERO study (M VT-601-3201) in the dossier.

The HERO study is an open-label, randomised, controlled phase III study comparing relugolix with leuprorelin, conducted at 160 study sites in Asia, Australia, Europe, North and South America, with a total of 1,078 patients, from April 2017 to November 2021.

Patients, who, in the opinion of the principal investigator, were eligible for at least 1 year of androgen deprivation therapy, had an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 1, and whose disease met the following criteria, were enrolled in the study:

- Evidence of biochemical (prostate specific antigen [PSA]) or clinical recurrence after initial curative local treatment and no candidate for surgical salvage therapy (hereafter referred to as group 1) or
- newly diagnosed, metastatic disease (hereafter referred to as group 2) or
- advanced, localised disease whose cure is unlikely through local initial treatment (surgery or radiation) with curative intent (hereinafter referred to as group 3).

Patients could not have had prior surgical castration and could not have been treated with a gonadotropin-releasing hormone (GnRH) analogue or other form of ADT (oestrogen or antiandrogen) for more than 18 months. For patients with a treatment duration ≤ 18 months, therapy had to be completed 3 months before the start of the study.

The total of 1,078 patients were randomised - stratified by region, presence of metastatic prostate cancer (mHSPC) and age at baseline (≤ 75 / > 75 years) - in a 2:1 ratio (relugolix n = 719, leuprorelin n = 359).

Treatment was given in both study arms for a maximum of 48 weeks or until unacceptable toxicity, dose interruption of relugolix > 10 days or withdrawal of consent. Treatment with

relugolix was administered in accordance with the marketing authorisation and the product information.

In addition to the primary endpoint of the study "sustained testosterone suppression at castration level", overall survival, endpoints on morbidity, health-related quality of life and adverse events (AEs) were collected as patient-relevant endpoints.

Relevant sub-population

For patient group b) of the present benefit assessment (patients with advanced HSPC who are ineligible for local therapy), the sub-population of patients without distant metastasis from the HERO study is used. This sub-population includes those patients from group 1 (biochemical or clinical recurrence after curative initial local treatment; ineligible for surgical salvage therapy) who do not have distant metastases and all patients from group 3 (advanced, localised disease unlikely to be cured by initial local treatment (surgery or radiation) with curative intent); in total, this sub-population includes 640 patients (relugolix n = 427; leuprorelin n = 213).

According to the inclusion criteria of the HERO study, patients in group 1 are ineligible for surgical salvage therapy and patients in group 3 are ineligible for surgery or radiation, but the inclusion criterion for patient group 1 does not indicate whether local salvage radiotherapy would still have been an option. For some of the patients in the sub-population from group 1 evaluated by the pharmaceutical company, there is thus uncertainty as to whether local (or specifically salvage) radiotherapy would still have been an option for them and whether the patients could have been assigned to other patient groups.

The exact percentage of patients for whom radiotherapy would still have been an option cannot be quantified. However, it can be assumed that the percentage of patients eligible for local therapy in the present setting is within a range that allows the pharmaceutical company's sub-population to be used for the patient group ineligible for local therapy.

Extent and probability of the additional benefit

Mortality

Overall survival

The endpoint of overall survival was defined in the HERO study as the time from randomisation to death from any cause. There are no signs of statistically significant differences between the treatment groups here. The number of deaths is low in both treatment groups at the present data cut-off. With regard to overall survival, an additional benefit of relugolix compared to leuprorelin is therefore not proven.

Morbidity

Symptomatology

Symptomatology was collected using the EORTC QLQ-C30 and EORTC QLQ-PR25 questionnaires. As part of the written statement procedure, the pharmaceutical company submits evaluations for deterioration by ≥ 10 points for the fatigue scale of the EORTC QLQ-C30 questionnaire and the scales for micturition disorder and hormone treatment-related symptoms of the EORTC QLQ-PR25 questionnaire. For all other scales of the two instruments, the pharmaceutical company does not submit any evaluations for deterioration by ≥ 10 points. For these scales, however, a response threshold of 15 points leads to the same change step

as a response threshold of 10 points. Therefore, for these scales, evaluations with a response threshold of 15 points are identical to evaluations with a response threshold of 10 points. Thus, with the statement and the dossier of the pharmaceutical company, evaluations are available for all scales of the EORTC QLQ-C30 and EORTC QLQ PR25 questionnaires that correspond to a response threshold of 10 points.

For the endpoint of diarrhoea assessed with the EORTC QLQ-C30 questionnaire, there is a statistically significant difference to the disadvantage of relugolix versus leuprorelin. There was no statistically significant difference between the treatment groups for any of the other endpoints on symptomatology measured with the EORTC QLQ-C30 and EORTC QLQ-PR25 questionnaires.

Health status

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. For the benefit assessment, the pharmaceutical company presented the responder analyses for the "time to permanent deterioration" by ≥ 15 points for this endpoint. However, there was no statistically significant difference between the treatment groups for this endpoint.

Quality of life

Health-related quality of life was collected using the EORTC QLQ-C30 and EORTC QLQ-PR25 questionnaires. As part of the written statement procedure, the pharmaceutical company submits evaluations for deterioration by ≥ 10 points for the physical functioning scale of the EORTC QLQ-C30 questionnaire. For all other scales of the two instruments, the pharmaceutical company does not submit any evaluations of the deterioration by ≥ 10 points. For these scales, however, a response threshold of 15 points leads to the same change step as a response threshold of 10 points. Therefore, for these scales, evaluations with a response threshold of 15 points are identical to evaluations with a response threshold of 10 points. Thus, with the statement and the dossier of the pharmaceutical company, evaluations are available for all scales of the EORTC QLQ-C30 and EORTC QLQ PR25 questionnaires that correspond to a response threshold of 10 points.

No suitable data are available for the endpoint of incontinence aid recorded with the EORTC QLQ-PR25 questionnaire. For all other endpoints on health-related quality of life measured with the EORTC QLQ-C30 and EORTC QLQ-PR25 questionnaires, there was no statistically significant difference between the treatment groups.

Side effects

Serious adverse events (SAEs), severe AEs, discontinuation due to AEs

For the endpoints of SAEs, severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) and discontinuation due to AEs, there were no statistically significant differences between the treatment groups.

Specific AEs

No specific AEs were selected.

Major Adverse Cardiovascular Event (MACE)

The combined endpoint of MACE is defined in the HERO study with the following individual components:

- any event leading to death
- "Non-fatal myocardial infarction" recorded using standardised MedDRA query (SMQ) "Myocardial infarction" (broad), excluding fatal events
- "Non-fatal central nervous system (CNS) haemorrhage and cerebrovascular diseases" recorded using the SMQ "Central nervous system haemorrhage and cerebrovascular diseases" (broad), excluding fatal events

In its statement, the pharmaceutical company provides further information on the MACE endpoint, including a sensitivity analysis in which the component "any event leading to death" was replaced by the component "cardiovascular events leading to death". According to the information provided by the pharmaceutical company, the classification as a cardiovascular event was made post hoc by clinical experts on the basis of the documented cause of death.

For the combined endpoint MACE, taking into account only SAEs or only severe AEs, there is a statistically significant difference to the advantage of relugolix over leuprorelin.

Overall assessment/ conclusion

For the assessment of the additional benefit of relugolix compared to leuprorelin in patients with advanced hormone-sensitive prostate cancer who are ineligible for local therapy, results from the open-label, randomised, controlled phase III HERO study are available for mortality (overall survival), morbidity (symptomatology and health status), health-related quality of life and side effects.

In the endpoint category of mortality, the present results for the endpoint of overall survival do not show any statistically significant difference between the treatment groups.

With regard to morbidity, the available results for the endpoints of symptomatology (assessed using EORTC QLQ-C30 and EORTC QLQ-PR25) and health status (assessed using EQ-5D VAS) do not show any differences between the treatment groups that are relevant for the benefit assessment.

In terms of quality of life, the results of the EORTC QLQ-C30 and EORTC QLQ-PR25 also show no statistically significant differences between the treatment groups.

In the side effects there also no statistically significant differences in SAEs, severe AEs and therapy discontinuations due to AEs.

With regard to the MACE endpoint, although the pharmaceutical company has resolved various uncertainties addressed in IQWiG's benefit assessment regarding the measurement reliability of this endpoint in its statement, other uncertainties remain. On the one hand, uncertainty remains as to whether local therapy would no longer have been an option for all patients in the sub-population presented by the pharmaceutical company. On the other, implausibilities arise with regard to the events included in the endpoint and their severity grades. According to the information provided by the pharmaceutical company in its statement, for example, the event of a transient ischaemic attack of CTCAE grade 3 is included in the evaluation as a severe AE, but according to the CTCAE there is no transient ischaemic attack of grade 3. In connection with the lack of adjudication, no advantage of relugolix over leuprorelin can therefore be derived.

In summary, neither advantages nor disadvantages can be identified for relugolix in all endpoint categories.

In the overall analysis of the available results, the G-BA therefore does not determine an additional benefit of relugolix compared to leuprorelin.

c) Patients with advanced hormone-sensitive prostate cancer and PSA recurrence or clinical recurrence after primary local therapy

An additional benefit is not proven.

Justification:

For the treatment of adult males with advanced hormone-sensitive prostate cancer and PSA recurrence or clinical recurrence after primary local therapy, the pharmaceutical company does not present any data for the assessment of additional benefit. Therefore, an additional benefit is not proven.

d) Patients with metastatic hormone-sensitive prostate cancer (mHSPC)

d1) Patients with metastatic hormone-sensitive prostate cancer (mHSPC) who are eligible for combination regimen

An additional benefit is not proven.

Justification:

For the treatment of adult males with metastatic hormone-sensitive prostate cancer who are eligible for combination regimen, the pharmaceutical company does not present any data for the assessment of additional benefit. Therefore, an additional benefit is not proven.

d2) Patients with metastatic hormone-sensitive prostate cancer (mHSPC) who are ineligible for combination regimen

An additional benefit is not proven.

Justification:

For the treatment of adult males with metastatic hormone-sensitive prostate cancer who are ineligible for combination regimen, the pharmaceutical company does not present any data for the assessment of additional benefit. Therefore, an additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Orgovyx with the active ingredient relugolix.

Relugolix is indicated for the treatment of adult males with advanced hormone-sensitive prostate cancer.

In the therapeutic indication under consideration, 5 patient groups were distinguished and the appropriate comparator therapy was determined as follows:

a) Patients with advanced hormone-sensitive prostate cancer who are eligible for local therapy

The appropriate comparator therapy includes radical prostatectomy (if necessary, in combination with lymphadenectomy) and percutaneous radiotherapy in combination with conventional ADT, bicalutamide or, for patients in clinical category cT3, HDR brachytherapy.

b) Patients with advanced hormone-sensitive prostate cancer who are ineligible for local therapy

The appropriate comparator therapy includes conventional androgen deprivation and bicalutamide.

c) Patients with advanced hormone-sensitive prostate cancer and PSA recurrence or clinical recurrence after primary local therapy

The appropriate comparator therapy includes both surgical and radiotherapeutic options of salvage therapy (if necessary, in combination with conventional androgen deprivation), which are available for a patient-individual treatment decision, taking into account the prior therapy and the risk of progression.

d) Patients with metastatic hormone-sensitive prostate cancer (mHSPC)

d1) Patients with metastatic hormone-sensitive prostate cancer (mHSPC) who are eligible for combination regimen

The appropriate comparator therapy comprises conventional androgen deprivation therapy with different combination partners.

d2) Patients with metastatic hormone-sensitive prostate cancer (mHSPC) who are ineligible for combination regimen

The appropriate comparator therapy comprises conventional androgen deprivation.

Assessment of the additional benefit for a)

No data are available to allow an assessment of the additional benefit. An additional benefit is not proven.

Assessment of the additional benefit for b)

For the benefit assessment, the pharmaceutical company presents the HERO study. In this randomised, open-label, controlled study, patients were randomised 2:1 to either the relugolix or leuprorelin arm. For patient group b) (patients with advanced hormone-sensitive prostate cancer who are ineligible for local therapy), the pharmaceutical company presents the results of a sub-population of the HERO study.

In the endpoint categories of overall survival and health-related quality of life, there were neither positive nor negative effects of relugolix compared to leuprorelin.

In the endpoint category of morbidity, there are no relevant differences for the benefit assessment overall.

In the endpoint category of side effects, there were neither positive nor negative effects for SAEs, severe AEs and therapy discontinuations due to AEs. For the MACE endpoint, there is a statistically significant difference to the advantage of relugolix, but an advantage of relugolix over leuprorelin cannot be inferred due to uncertainties.

Overall, it is therefore concluded that there is no evidence of an additional benefit of relugolix over leuprorelin in the treatment of patients with advanced hormone-sensitive prostate cancer who are ineligible for local therapy.

Assessment of the additional benefit for c)

No data are available to allow an assessment of the additional benefit. An additional benefit is not proven.

Assessment of the additional benefit for d1)

No data are available to allow an assessment of the additional benefit. An additional benefit is not proven.

Assessment of the additional benefit for d2)

No data are available to allow an assessment of the additional benefit. An additional benefit 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. This information is subject to uncertainties, which are explained below for the individual patient groups with the main reasons.

For patient group a), the information provided by the pharmaceutical company is to be classified as underestimated. On the one hand, the incidence as a starting point does not take into account those patients who were under active surveillance in previous years and are eligible for local therapy for the first time in the year under review. Furthermore, the pharmaceutical company does not use a majority of patients with advanced prostate cancer (patients with localised prostate cancer and a high risk of developing a relapse).

For patient group b), the data are assessed as uncertain overall. The pharmaceutical company assumes that these patients are characterised by the fact that ADT as monotherapy is recommended for them. This implies that local therapy is not an option only for these patients. However, the pharmaceutical company does not take into account the fact that ADT can also be carried out in combination with local therapy when implementing its derivation of the number of patients in this patient group.

The data on patient group c) are also associated with uncertainties. Due to incorrect transfer of the percentage values as well as uncertainties regarding the values used from the DKG report, an underestimation as well as an overestimation can be assumed here.

The methodological procedure of the pharmaceutical company when calculating the percentage values for patient group d) is subject to considerable uncertainties. These lie in particular in the transferability of the sources used by the pharmaceutical company to the German healthcare context.

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 Orgovyx (active ingredient: relugolix) at the following publicly accessible link (last access: 23 March 2023):

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

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

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 March 2023).

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

Inpatient treatments

Some treatment options of the appropriate comparator therapy are carried out on an inpatient basis. The inpatient costs are calculated on the basis of the case flat fee revenues, which result from the valuation ratios of the respective DRG multiplied by the federal base rate value of 2022 (€ 3,833.07). Furthermore, the nursing revenue is included in the inpatient costs. This is calculated from the average length of stay of the concerned DRG multiplied by the nursing fee Section 15 para. 2a KHEntgG (Act on Fees for Full and Semi-inpatient Hospital Services) (July till December 2022: 200 €) and the treatment-specific nursing revenue valuation ratio.

The calculation of the costs of the inpatient treatments is standardised in the following on the basis of the DRG case flat fee catalogue 2022 and the nursing revenue catalogue 2022, the base rate value of 2022 as well as the nursing fee value pursuant to Section 15, paragraph 2a (Act on Fees for Full and Semi-inpatient Hospital Services), since the federal base rate value for 2023 was not yet available at the time of the cost calculation (15 March 2023).

Radiotherapy

According to the guideline, percutaneous radiotherapy involves a dose of at least 74.0 Gy to approximately 80 Gy, with the standard single dose being 1.8 Gy to 2.0 Gy.[2] This results in 37 to 45 treatment days for this treatment option.

[2] S3 Guideline Prostate Cancer, V.6.2, October 2021, AWMF Reg.no.: 034/022OL https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Prostatatkarzinom/Version_6/LL_Prostatakarzinom_Langversion_6.2.pdf

For salvage radiotherapy, the guideline recommends a minimum total dose of 66 Gy with single doses of 1.8 Gy to 2.0 Gy.[2] This results in 33 to 37 treatment days.

Treatment period:

a) Patients with advanced hormone-sensitive prostate cancer who are eligible for local therapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Relugolix	Continuously, 1 x daily	365	1	365.0
Appropriate comparator therapy				
Radical prostatectomy, if necessary + lymphadenectomy				
Radical prostatectomy if necessary + lymphadenectomy	once		7.7 - 8.6 (average length of stay)[3]	-
Percutaneous radiotherapy + conventional androgen deprivation or bicalutamide				
Percutaneous radiotherapy	once		37 - 45	37.0 – 45.0
Conventional androgen deprivation				
Buserelin	Continuously, every 3 months	4	1	4.0
Goserelin	Continuously, every 3 months	4	1	4.0
Leuprorelin	Continuously, every 3 months	4	1	4.0
Triptorelin	Continuously, every 6 months	2	1	2.0
Degarelix	Continuously, 1 x monthly	12	1	12.0
Orchiectomy	once		3.8 (average length of stay)[3]	-
Bicalutamide	Continuously, 1 x daily	365	1	365.0
Percutaneous radiotherapy + HDR brachytherapy (only for patients in category cT3)				
Percutaneous radiotherapy	once		37 - 45	37.0 - 45.0

[3] Case flat fee Catalogue and Nursing Revenue Catalogue 2022 https://www.g-drg.de/ag-drg-system-2022/fallpauschalen-katalog/fallpauschalen-katalog-2022, accessed on 20.02.2023

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
HDR brachytherapy	once		4.8 (average length of stay)[3]	-

b) Patients with advanced hormone-sensitive prostate cancer who are ineligible for local therapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Relugolix	Continuously, 1 x daily	365	1	365.0
Appropriate comparator therapy				
Conventional androgen deprivation				
Buserelin	Continuously, every 3 months	4	1	4.0
Goserelin	Continuously, every 3 months	4	1	4.0
Leuprorelin	Continuously, every 3 months	4	1	4.0
Triptorelin	Continuously, every 6 months	2	1	2.0
Degarelix	Continuously, 1 x monthly	12	1	12.0
Orchiectomy	once		3.8 (average length of stay)Fehler! Textmarke nicht definiert.	-
Bicalutamide				
Bicalutamide	Continuously, 1 x daily	365	1	365.0

c) Patients with advanced hormone-sensitive prostate cancer and PSA recurrence or clinical recurrence after primary local therapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Relugolix	Continuously, 1 x daily	365	1	365.0
Appropriate comparator therapy				
Patient-individual therapy taking into account prior therapy and risk of progression				
Salvage prostatectomy				
Salvage prostatectomy	once		7.7 - 8.6 (average length of stay)[3]	-
Percutaneous salvage radiotherapy				
Percutaneous salvage radiotherapy	once		33 - 37	33.0 - 37.0
Percutaneous salvage radiotherapy + conventional androgen deprivation or bicalutamide				
Percutaneous salvage radiotherapy	once		33 - 37	33.0 - 37.0
Conventional androgen deprivation				
Buserelin	Continuously, every 3 months	4	1	4.0
Goserelin	Continuously, every 3 months	4	1	4.0
Leuprorelin	Continuously, every 3 months	4	1	4.0
Triptorelin	Continuously, every 6 months	2	1	2.0
Degarelix	Continuously, 1 x monthly	12	1	12.0
Orchiectomy	once		3.8 (average length of stay)[Fehler! Textmarke nicht definiert.]	-
Bicalutamide	Continuously, 1 x daily	365	1	365.0

d) Patients with metastatic hormone-sensitive prostate cancer (mHSPC)

d1) Patients with metastatic hormone-sensitive prostate cancer (mHSPC) who are eligible for combination regimen

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Relugolix	Continuously, 1 x daily	365	1	365.0
Appropriate comparator therapy				
Conventional androgen deprivation + apalutamide				
Conventional androgen deprivation				
Buserelin	Continuously, every 3 months	4	1	4.0
Goserelin	Continuously, every 3 months	4	1	4.0
Leuprorelin	Continuously, every 3 months	4	1	4.0
Triptorelin	Continuously, every 6 months	2	1	2.0
Degarelix	Continuously, 1 x monthly	12	1	12.0
Orchiectomy	once		3.8 (average length of stay)Fehler! Textmarke nicht definiert.	-
Apalutamide	Continuously, 1 x daily	365	1	365.0
Conventional androgen deprivation + abiraterone acetate and prednisone or prednisolone				
Conventional androgen deprivation				
Buserelin	Continuously, every 3 months	4	1	4.0
Goserelin	Continuously, every 3 months	4	1	4.0
Leuprorelin	Continuously, every 3 months	4	1	4.0
Triptorelin	Continuously, every 6 months	2	1	2.0
Degarelix	Continuously, 1 x monthly	12	1	12.0
Orchiectomy	once		3.8 (average length of stay)Fehler! Textmarke nicht definiert.	-

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Abiraterone acetate	Continuously, 1 x daily	365	1	365.0
Prednisone	Continuously, 1 x daily	365	1	365.0
Prednisolone	Continuously, 1 x daily	365	1	365.0
Conventional androgen deprivation + docetaxel with or without prednisone or prednisolone				
Conventional androgen deprivation				
Buserelin	Continuously, every 3 months	4	1	4.0
Goserelin	Continuously, every 3 months	4	1	4.0
Leuprorelin	Continuously, every 3 months	4	1	4.0
Triptorelin	Continuously, every 6 months	2	1	2.0
Degarelix	Continuously, 1 x monthly	12	1	12.0
Orchiectomy	once		3.8 (average length of stay)[Fehler! Textmarke nicht definiert.]	-
Docetaxel	1 x every 21 days	6	1	6.0
Prednisone	2 x daily	6	21	126.0
Prednisolone	2 x daily	6	21	126.0
Conventional androgen deprivation + enzalutamide				
Conventional androgen deprivation				
Buserelin	Continuously, every 3 months	4	1	4.0
Goserelin	Continuously, every 3 months	4	1	4.0
Leuprorelin	Continuously, every 3 months	4	1	4.0
Triptorelin	Continuously, every 6 months	2	1	2.0
Degarelix	Continuously, 1 x monthly	12	1	12.0
Orchiectomy	once		3.8 (average length of	-

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
			stay)[Fehler! Textmarke nicht definiert.]	
Enzalutamide	Continuously, 1 x daily	365	1	365.0

d2) Patients with metastatic hormone-sensitive prostate cancer (mHSPC) who are ineligible for combination regimen

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Relugolix	Continuously, 1 x daily	365	1	365.0
Appropriate comparator therapy				
Conventional androgen deprivation				
Conventional androgen deprivation				
Buserelin	Continuously, every 3 months	4	1	4.0
Goserelin	Continuously, every 3 months	4	1	4.0
Leuprorelin	Continuously, every 3 months	4	1	4.0
Triptorelin	Continuously, every 6 months	2	1	2.0
Degarelix	Continuously, 1 x monthly	12	1	12.0
Orchiectomy	once		3.8 (average length of stay)[Fehler! Textmarke nicht definiert.]	-

Consumption:

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

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

The average body measurements of adult males were applied for dosages depending on body weight or body surface area (average body height: 1.79 m; average body weight: 85 kg).[4] This results in a body surface area of 2.04 m² (calculated according to Du Bois 1916.[5]

a) Patients with advanced hormone-sensitive prostate cancer who are eligible for local therapy

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					
Relugolix	120 mg	120 mg	1 x 120 mg	365.0	365.0 x 120 mg
Appropriate comparator therapy					
Radical prostatectomy, if necessary + lymphadenectomy					
Radical prostatectomy if necessary + lymphadenectomy	One-off intervention				
Percutaneous radiotherapy + conventional androgen deprivation or bicalutamide					
Percutaneous radiotherapy	1.8 Gy - 2.0 Gy	1.8 Gy - 2.0 Gy	1.8 Gy - 2.0 Gy	37.0 - 45.0	74.0 Gy - 80.0 Gy
Conventional androgen deprivation					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4.0 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4.0 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4.0 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2.0 x 22.5 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12.0 x 80 mg
Orchiectomy	One-off intervention				
Bicalutamide	150 mg	150 mg	3 x 50 mg	365.0	1095.0 x 50 mg
Percutaneous radiotherapy + HDR brachytherapy (only for patients in category cT3)					
Percutaneous radiotherapy	1.8 Gy - 2.0 Gy	1.8 Gy - 2.0 Gy	1.8 Gy - 2.0 Gy	37 - 45	74.0 Gy - 80.0 Gy
HDR brachytherapy	One-off intervention				

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

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

b) Patients with advanced hormone-sensitive prostate cancer who are ineligible for local therapy

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					
Relugolix	120 mg	120 mg	1 x 120 mg	365.0	365.0 x 120 mg
Appropriate comparator therapy					
Conventional androgen deprivation					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4.0 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4.0 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4.0 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2.0 x 22.5 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12.0 x 80 mg
Orchiectomy	One-off intervention				
Bicalutamide					
Bicalutamide	150 mg	150 mg	3 x 50 mg	365.0	1,095.0 x 50 mg

c) Patients with advanced hormone-sensitive prostate cancer and PSA recurrence or clinical recurrence after primary local therapy

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					
Relugolix	120 mg	120 mg	1 x 120 mg	365.0	365.0 x 120 mg
Appropriate comparator therapy					
Patient-individual therapy taking into account prior therapy and risk of progression					
Salvage prostatectomy					
Salvage prostatectomy	One-off intervention				
Percutaneous salvage radiotherapy					
Percutaneous salvage radiotherapy	1.8 Gy - 2.0 Gy	1.8 Gy - 2.0 Gy	1.8 Gy - 2.0 Gy	33 - 37	≥ 66.0 Gy

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Percutaneous salvage radiotherapy + conventional androgen deprivation or bicalutamide					
Percutaneous salvage radiotherapy	1.8 Gy - 2.0 Gy	1.8 Gy - 2.0 Gy	1.8 Gy - 2.0 Gy	33 - 37	≥ 66.0 Gy
Conventional androgen deprivation					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4.0 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4.0 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4.0 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2.0 x 22.5 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12.0 x 80 mg
Orchiectomy	One-off intervention				
Bicalutamide	150 mg	150 mg	3 x 50 mg	365.0	1,095.0 x 50 mg

d) Patients with metastatic hormone-sensitive prostate cancer (mHSPC)

d1) Patients with metastatic hormone-sensitive prostate cancer (mHSPC) who are eligible for combination regimen

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					
Relugolix	120 mg	120 mg	1 x 120 mg	365.0	365.0 x 120 mg
Appropriate comparator therapy					
Conventional androgen deprivation + apalutamide					
Conventional androgen deprivation					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4.0 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4.0 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4.0 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2.0 x 22.5 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12.0 x 80 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
Orchiectomy	One-off intervention				
Apalutamide	240 mg	240 mg	4 x 60 mg	365.0	1,460.0 x 60 mg
Conventional androgen deprivation + abiraterone acetate and prednisone or prednisolone					
Conventional androgen deprivation					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4.0 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4.0 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4.0 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2.0 x 22.5 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12.0 x 80 mg
Orchiectomy	One-off intervention				
Abiraterone acetate	1000 mg	1000 mg	2 x 500 mg	365.0	730.0 x 500 mg
Prednisone	5 mg	5 mg	1 x 5 mg	365.0	365.0 x 5 mg
Prednisolone	5 mg	5 mg	1 x 5 mg	365.0	365.0 x 5 mg
Conventional androgen deprivation + docetaxel with or without prednisone or prednisolone					
Conventional androgen deprivation					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4.0 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4.0 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4.0 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2.0 x 22.5 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12.0 x 80 mg
Orchiectomy	One-off intervention				
Docetaxel	75 mg/m^2 = 153 mg	153 mg	2 x 80 mg	6.0	12.0 x 80 mg
Prednisone	5 mg	10 mg	2 x 5 mg	126.0	252.0 x 5 mg
Prednisolone	5 mg	10 mg	2 x 5 mg	126.0	252.0 x 5 mg
Conventional androgen deprivation + enzalutamide					
Conventional androgen deprivation					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4.0 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4.0 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4.0 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2.0 x 22.5 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12.0 x 80 mg
Orchiectomy	One-off intervention				
Enzalutamide	160 mg	160 mg	4 x 40 mg	365	1,460.0 x 40 mg

d2) Patients with metastatic hormone-sensitive prostate cancer (mHSPC) who are ineligible for combination regimen

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					
Relugolix	120 mg	120 mg	1 x 120 mg	365.0	365.0 x 120 mg
Appropriate comparator therapy					
Conventional androgen deprivation					
Conventional androgen deprivation					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4.0 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4.0 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4.0 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2.0 x 22.5 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12.0 x 80 mg
Orchiectomy	One-off intervention				

Costs:

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

Inpatient treatments

Calculation year	DRG	Average length of stay [d]	DRG valuation ratio (main department)	Federal base case value	Nursing revenue valuation ratio	Nursing fee	Case flat fee revenue	Nursing revenue	Total case flat fee revenue and nursing revenue
Appropriate comparator therapy									
Radical prostatectomy, if necessary + lymphadenectomy									
2022	M04A	8.6	2.078	€ 3,833.07	0.8004	€ 200	€ 7,965.12	€ 1,376.69	€ 9,341.81
2022	M01B	7.7	2.371	€ 3,833.07	0.7106	€ 200	€ 9,088.21	€ 1,094.32	€ 10,182.53

HDR brachytherapy									
2022	M10C	4.8	1.118	€ 3,833.07	0.8247	€ 200	€ 4,285.37	€ 791.71	€ 5,077.08
Salvage prostatectomy									
2022	M04A	8.6	2.078	€ 3,833.07	0.8004	€ 200	€ 7,965.12	€ 1,376.69	€ 9,341.81
Orchiectomy									
2022	M04B	3.8	0.886	€ 3,833.07	0.7676	€ 200	€ 3,396.10	€ 583.38	€ 3,979.48

Radiotherapy

Designation of the therapy	Designation of the service	Number	Costs/ unit	Costs / patient / year
Appropriate comparator therapy				
Percutaneous radiotherapy	Irradiation with a linear accelerator for malignant diseases or space-occupying processes of the central nervous system (GOP 25321)	37 - 45	€ 110.32	€ 4,081.84 - € 4,964.40
Percutaneous salvage radiotherapy	Irradiation with a linear accelerator for malignant diseases or space-occupying processes of the central nervous system (GOP 25321)	33 - 37	€ 110.32	€ 3,640.56 - € 4,081.84

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Relugolix 120 mg	30 FCT	€ 231.23	€ 2.00	€ 20.88	€ 208.35
Appropriate comparator therapy					
Abiraterone acetate 500 mg	56 FCT	€ 291.95	€ 2.00	€ 13.32	€ 276.63
Apalutamide 60 mg	112 FCT	€ 2,831.39	€ 2.00	€ 113.15	€ 2,716.24
Bicalutamide 50 mg [6]	90 FCT	€ 156.64	€ 2.00	€ 11.50	€ 143.14
Buserelin 9.45 mg 3-month implant	2 PS	€ 1,028.11	€ 2.00	€ 96.51	€ 929.60

[6] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Degarelix 80 mg	3 PSI	€ 591.85	€ 2.00	€ 55.10	€ 534.75
Docetaxel 80 mg	1 CIS	€ 415.86	€ 2.00	€ 19.20	€ 394.66
Enzalutamide 40 mg	112 FCT	€ 3,193.29	€ 2.00	€ 127.91	€ 3,063.38
Goserelin 10.8 mg 3-month implant	2 IMP	€ 1,013.52	€ 2.00	€ 95.13	€ 916.39
Leuprorelin 11.25 mg 3-month implant	2 IMP	€ 730.74	€ 2.00	€ 86.93	€ 641.81
Prednisone 5 mg [6]	100 TAB	€ 16.71	€ 2.00	€ 0.43	€ 14.28
Prednisolone 5 mg[6]	100 TAB	€ 15.40	€ 2.00	€ 0.33	€ 13.07
Triptorelin 22.5 mg	1 DSS	€ 1,006.38	€ 2.00	€ 94.45	€ 909.93
Abbreviations: PS = prefilled syringes; FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; IMP = implant; PSI = powder and solvent for solution for injection; TAB = tablets; DSS = dry substance with solvent					

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Costs for additionally required SHI services:

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

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

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

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active

ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Relugolix

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 12 April 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 13 December 2022, the pharmaceutical company submitted a dossier for the benefit assessment of relugolix to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 14 October 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 relugolix.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 January 2023, and the written statement procedure was initiated with publication on the G-BA website on 16 January 2023. The deadline for submitting written statements was 6 February 2023.

The oral hearing was held on 20 February 2023.

On 2 March 2023, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 1.1 dated 1 March 2023 replaces version 1.0 of the dossier assessment dated 12 January 2023. The assessment result was not affected by the changes in version 1.1 compared to version 1.0.

By letter dated 21 February 2023, 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 10 March 2023.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 28 March 2023, and the proposed resolution was approved.

At its session on 6 April 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	12 April 2022	Determination of the appropriate comparator therapy
Working group Section 35a	14 February 2023	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	20 February 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	28 February 2023 14 March 2023 21 March 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee on Medicinal Products	28 March 2023	Concluding discussion of the draft resolution
Plenum	6 April 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 6 April 2023

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

Prof. Hecken